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Current therapies and pharmacy programs for obesity and diabetes

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A growing body of Australian and international literature has reported the benefits and improved health outcomes resulting from various trials of pharmaceutical care, self-management support and other cognitive services in chronic conditions such as diabetes and obesity. This review will focus on existing medications, the reasons why they might not work for some individuals and the potential for new ways to treat both diseases. It will also review novel ways to manage the diseases, including using community pharmacy as a site for intervention, once effective therapies are available.

The burden of diabetes and obesity for individuals and for the community is high. The complications of both diseases are related and of the order that adequate treatment and control are vital to limit an epidemic of severe morbidity and mortality. Medications and how they are used play a key role in the management of these chronic conditions. Current antidiabetic therapies enhance insulin secretion by pancreatic beta-cells, reducing insulin resistance, modulating glucose metabolism or in type 1 diabetes or refractory type 2 diabetes, replacing insulin. Although several subclasses of non-insulin agents have been in use for some time, detailed information on their modes of action, use in various combinations and factors that prevent their optimal use are only recently emerging and require further understanding. Pharmacotherapy is also being increasingly used as a component of preventive programs targeting insulin resistance and obesity before onset of diabetes ('prediabetes'), especially in children and adolescents. Pharmacists contribute significantly to quality use of medicines when they provide information, advice and recommendations to patients and providers to optimise therapeutic outcomes. In recent years, pharmacists have also sought to develop an expanded role in contributing to the management of chronic diseases to meet the needs of this growing patient population.

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Diabetes

Type 2 diabetes mellitus (T2DM), the most common form of diabetes, is now an escalating worldwide epidemic. It contributes significantly to premature mortality, morbidity and disability through the development of micro- and macrovascular complications of uncontrolled disease. In Australia, the 2007–2008 National Health Survey estimated that 818 200 Australians (4%) have diabetes, based on self-reports [1]. The earlier national Australian Diabetes, Obesity and Lifestyle study found that approximately 1.2 million (7.4%) of Australians aged 25 years and over had diabetes with half of the respondents unaware [1]. A further 16% of Australians have been estimated to have impaired glucose metabolism or prediabetes [2]. The total economic burden is estimated at A$6 billion annually (2003) arising mainly from the costs associated with the treatment of complications [3].

The incidence and prevalence of T2DM in adolescents is increasing globally, but especially in those of non-white European descent [4]. The International Diabetes Federation estimates that 285 million people around the world have diabetes. This total is expected to rise to 438 million within 20 years. Highest risk groups are those of black African descent, native North American, Hispanic, Asian, South Asian and Native Pacific Islanders. These groups have higher genetic risk factors with the clinical expression of T2DM being accelerated by increasing rates of childhood and adolescent overweight and obesity [5]. While T2DM is being seen in increasing prevalence in younger age groups, it is rarely seen until the second decade of life since it requires the trigger of the physiological increase in insulin resistance that occurs with puberty [4].

Obesity

Obesity is a major global public health and economic problem as it is associated with significant morbidity and mortality. In 2005, the World Health Organisation reported approximately 1.6 billion adults as overweight; 400 million of those were obese [6]. Australia is one of the most overweight developed nations [7], with a growing incidence over the last 12 years, approximately 68% of adult men and 55% of adult women were overweight or obese in 2007–2008 [8]. The total cost of obesity in 2008 was A$58.2 billion which included the costs attributable to associated diseases [9].

Overweight and obesity are both disease states and risk factors for many other chronic conditions. Overweight is defined as a body mass index (BMI) ≥25 in adults or 85th percentile in children and adolescents and obesity as a body mass index ≥30 in adults or the 95th percentile in children and adolescents. Higher body mass was responsible for 7.5% of the total burden of disease and injury in 2003, ranked behind tobacco (7.8%) and high blood pressure (7.6%) [10].

Excess body mass predicts higher mortality and/or morbidity in cardiovascular disease, T2DM, some cancers and increasingly, osteoarthritis [11]. Obesity is also strongly associated with back, reproductive and mental health problems, and obstructive sleep apnoea. Modest weight losses of 5% to 10% have been shown to improve hypertension and dyslipidaemia [10, 12].

In response to this problem the Australian Government recommended in June 2009, strategies for the treatment, management and prevention of obesity in 'Weighing it up – obesity in Australia', as well as better regulation of weight-loss products and programs to ensure safety and efficacy[9].

Addressing the problems

Evidence-based strategies addressing the problem of T2DM support the benefits of early interventions in prediabetes and strict control of glycaemia, blood pressure and lipids in established diabetes to reduce the risk and delay the onset of the complications such a cardiovascular and kidney disease [13–15]. In recent years, a plethora of clinical and management guidelines which recommend therapeutic targets to optimise disease control have become widely available to healthcare practitioners. This, coupled with advances in understanding of the pathophysiology of T2DM and the introduction of a range of new management therapies in the past decade, have ushered in the possibility of reducing the disease burden associated with T2DM and its complications.

There is broad agreement that the most appropriate first-line therapy for overweight and obesity in all age groups is behavioural and lifestyle interventions, including nutritional and exercise interventions [16]. This is particularly so in children and adolescents in whom the problem is generally less entrenched and has fewer complications. Also, there is lower availability of licensed drugs for the use of obesity in children and adolescents and greater reluctance to use pharmacotherapy in the young because of concern about long-term side effects. The lessons of history have shown these concerns to be justified.

Management of T2DM

The clinical management of T2DM aims to achieve control of glycaemia, as well as other risk factors such as blood pressure, dyslipidaemia and obesity to prevent or reduce the progression of the micro- and macrovascular complications associated with the condition. Initial and then ongoing management involves recommended modifications to diet and physical activity to address blood glucose as well as cholesterol and blood pressure. For blood glucose, if satisfactory glycaemic control is not achieved through weight loss and increased physical activity alone, pharmacotherapy is indicated. The current guidelines recommend that pharmacological therapy is commenced with metformin [17]. However, over time beta-cell function progressively declines, usually necessitating the addition of additional agents which include sulfonylureas, meglitinides, thiazolidinediones, and potentially incretin mimetics such as the oral DPPIV inhibitors, injectable agents such as exenatide, or insulin. The therapeutic use of each of these classes is discussed in the next section.

T2DM is a complex condition to manage, requiring all elements of the biopsychosocial model to be considered. Addressing lifestyle issues such as diet and exercise, as well as care in commencing and up-titrating medications, and vigilance in monitoring of the disease including achieving and sustaining blood glucose and other targets in therapy, is demanding

on the person with diabetes, their families and on healthcare resources. The membership of the health professional team that supports the person with T2DM is broad, and depending upon individual patient's needs may include the general practitioner, practice nurse and dietitian, as well as the diabetes nurse educator, specialist endocrinologist, podiatrist, optometrist, ophthalmologist and psychologist. As described in later parts of this chapter the pharmacist can, and should, be an integral member of the healthcare team supporting the care of the person with diabetes.

The rest of this chapter will focus on pharmacotherapy for blood glucose in T2DM and pharmacotherapy in obesity, and management of these diseases in adults and adolescents. Commercial programs available for obesity management will be discussed, as well as optimising management of T2DM and obesity in our current health system and the evidence and potential role of pharmacy in improving outcomes for these diseases.

Optimisation of current therapies for diabetes

Current antidiabetic agents enhance the secretion of insulin by pancreatic beta-cells, improve insulin resistance in tissues or modulate glucose metabolism. Although several classes of drugs have been used in the treatment of diabetes for some time it is only recently that detailed information on their modes of action and the factors that prevent their optimal use in patients have emerged.

Major classes of antidiabetic agents

(a) Insulin secretagogues

ATP is generated during mitochondrial glucose metabolism and modulates the opening of ATP-sensitive potassium channels on the plasma membrane. These channels are composed of eight polypeptides: four sulfonylurea receptor (SUR1) subunits that are members of the ATP-binding cassette transporter family and four Kir6 subunits that are members of the inwardly rectifying potassium channel family [18]. Hypoglycaemic sulfonylureas, such as glibenclamide, glipizide and tolbutamide, stimulate insulin secretion by interaction with SUR1. SUR1-induced closure of the ATP-sensitive potassium channel mediated by sulfonylureas depolarises the plasma membrane and promotes the release of insulin [19].

The meglitinides, such as repaglinide and nateglinide, are non-sulfonylurea insulin secretagogues whose mechanism of action resembles that of the sulfonylureas but is mediated through a different binding site on SUR1 [20]. Unlike the sulfonylureas, the meglitinides stimulate first-phase insulin release in a glucose-sensitive manner [21]. These properties enhance the control of serum glucose and insulin concentrations.

(b) Insulin sensitisers

The storage of lipid in adipocytes and other cells is dysregulated in T2DM and desensitises insulin signalling. As a result, adipocytes do not store triglycerides adequately or release adipokines that regulate food intake. Thiazolidinediones are agonists for the nuclear

peroxisome proliferator-activated receptor-gamma (PPAR-gamma), which regulates lipid storage in adipocytes [22]. These agents enhance insulin sensitivity by modulating the production of adipokines, including leptin, adiponectin, resistin and tumour necrosis factor-alpha, by adipocytes. By activating PPAR-gamma thiazolidinediones alter the transcription of genes that regulate glucose and lipid metabolism, such as lipoprotein lipase, fatty acyl-CoA synthase, glucokinase and the glucose transporter GLUT4.

Although PPAR-gamma appears to be an important target for thiazolidinediones the receptor is expressed primarily in adipocytes. That these drugs improve insulin resistance in other cells that do not express PPAR-gamma suggests that there may be additional targets. Thus, thiazolidinediones may also target the adenosine monophosphate-activated protein kinase (AMPK), which is an important fuel sensor that regulates glucose and lipid metabolism.

(c) Biguanides

The most important biguanide in current use is metformin but its mechanism of action is not entirely clear. In diabetic patients metformin decreases hepatic glucose output by decreasing gluconeogenesis and by increasing glucose uptake by skeletal muscle. However, it has also been shown that metformin activates AMPK in liver and muscle [23]. AMPK inhibits acetyl-coenzyme A carboxylase, which is the rate-limiting step of lipogenesis and down-regulates hepatic sterol-regulatory-element-binding-protein-1, which is a major regulator of lipogenic genes. This decreases triglyceride synthesis and facilitates the normalisation of lipid and glucose metabolism.

(d) Incretin mimetics

Exenatide is the only drug in this group currently available in Australia. Exenatide binds to the human GLP-1 receptor, which provides glycaemic control via various mechanisms [24]. It is an insulin secretagogue that stimulates glucose dependent insulin secretion and therefore only works during hyperglycaemia but not during hypoglycaemia. The functioning of pancreatic beta-cells in patients with T2DM may also be improved by exenatide [24]. The secretion of glucagon is suppressed by exenatide, which lowers the blood glucose levels in both fasting and postprandial periods.

Furthermore, exenatide delays gastric emptying in patients with T2DM [24]. This is very important in the regulation of postprandial blood glucose control, since the latter is strongly determined by the delivery of nutrients from the stomach to the small intestine. Exenatide also suppresses appetite, leading to a reduction in food intake and a decrease in body weight in the longer term usually of some kilograms.

It is indicated in Australia as adjunctive therapy to improve glycaemic control in patients with T2DM who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control.

(e) DPP-IV inhibitors

Another new class of oral antidiabetic agents are the dipeptidyl peptidase IV inhibitors (DPP-IV) or 'incretin enhancers'. They work by delaying the degradation of GLP-1 and thus extend the action of insulin in a glucose dependent manner, while also suppressing the release of glucagon [24]. There are currently three agents in this class approved in Australia: saxagliptin, sitagliptin and vildagliptin.

(f) Alpha-glucosidase inhibitors

These agents, acarbose and miglitol, are taken orally and slow absorption of glucose by inhibiting alpha-glucosidases in the upper GI tract. These enzymes are responsible for converting complex polysaccharide carbohydrates into monosaccharides in a dose dependent fashion. They are less potent than other oral agents with an HbA1c lowering effect of 0.4% to 0.9% generally reported and are usually used in combination with other agents rather than as monotherapy [25].

(g) Insulin

Historically, insulin has been used late in the therapeutic cascade in T2DM after trial and failure to achieve targets through lifestyle modification and oral medications. Since decline in beta-cell function and reduced effectiveness of other agents over time is common in the pathophysiology of T2DM, many if not most patients will require insulin therapy, usually within ten years of the diagnosis of T2DM. In general, physicians have been reluctant to add insulin to therapy because of concerns about increased complexity, risk of hypoglycaemia and patient acceptance, and the possible need to commence insulin injections has been used as a motivator or 'threat' to improve lifestyle factors [26]. Yet insulin is the most efficacious agent to lower blood glucose levels in diabetes mellitus. A variety of insulin regimens are employed including simple basal supplements (with isophane, insulin-glargine or insulin-detemir) to suppress hepatic glucose production, with the addition of prandial doses (regular human insulin or rapid-acting analogue) if needed to control meal-related hyperglycaemia. Premixed insulin combinations are also frequently used. To date, insulin pump therapy has not been generally recommended as a means of insulin delivery in T2DM because simpler injection regimens are effective and cheaper; however increasing use is likely in subgroups with T2DM who have blood glucose levels that are difficult to stabilise.

(h) Combination therapy

The agents outlined above are frequently used in combination, especially if glycaemic targets are not being met with single agents. As yet, there is no clear evidence as to which combinations are most effective or the order in which they are used and often the decision relates to individual patient factors and physician preference. The American Diabetes Association and the European Association for the Study of Diabetes have published a consensus algorithm for the metabolic management of T2DM [27]. The NHMRC of Australia has also published an algorithm as part of the *Evidence-based clinical care*

guidelines in blood glucose control in type 2 diabetes [28]. In each of these guidelines, metformin is a cornerstone of therapy, often with the addition of a secretagogue agent as a second line and then the addition or substitution of insulin. A number of combination medications are available that combine metformin with a sulphonylurea, or with a DPP-IV inhibitor. We can expect changes in these drug therapy paradigms as experience is gained with newer agents such as incretin mimetics and the safety concerns with other agents (eg thiazolidinediones) are clarified.

Adverse effects of current therapies and pharmacokinetic considerations

(a) Insulin secretagogues

The major side effect of sulfonylureas and meglitinides is hypoglycaemia, but this is usually mild and by definition is self-treated. Additional adverse effects of meglitinides include upper respiratory tract infections, rhinitis, bronchitis, dizziness and headache.

Pharmacokinetic studies have shown that serum concentrations of sulfonylureas and meglitinides are subject to marked inter-individual variation. Hepatic cytochromes P450 (CYPs) 2C8, 2C9 and 2C19 mediate the phase I oxidation of most of these drugs. These CYPs exhibit polymorphisms that give rise to altered drug pharmacokinetics. The two major variant alleles of CYP2C9 – CYP2C9*2 and CYP2C9*3 – occur at frequencies of ~11% and ~7%, respectively, in Caucasians, but exhibit lower incidence in African-Americans and Asians [29]. These CYP2C9 polymorphisms influence the apparent clearance of tolbutamide, glimepiride and glibenclamide and may complicate therapy in Caucasians in particular [29]. In contrast, *in vivo* pharmacokinetics of gliclazide were dependent on CYP2C19. The poor metaboliser phenotype for CYP2C19 is important in Asians due to the higher incidence of defective CYP2C19*2 and *3 alleles (~20% in Asians, but only 2% in Caucasians).

Repaglinide is eliminated by CYP2C8 and, to a lesser extent, CYP3A4-mediated oxidation to inactive phase I metabolites and by UDP-glucuronosyltransferases to the acyl glucuronide [30]. The CYP2C8*1/*3 genotype has been associated with decreased plasma concentrations of repaglinide. In comparison, nateglinide is metabolised by CYP2C9 and CYP3A4. However, the concordance between CYP2C alleles and the pharmacodynamics of these drugs is imperfect [29], and CYP2C genotyping to direct drug and dose selection is not currently indicated.

(b) Insulin sensitisers

Adverse effects of thiazolidinediones such as rosiglitazone and pioglitazone include weight gain and increase in peripheral fat mass, oedema, anaemia, pulmonary oedema, congestive heart failure and myocardial ischaemia [31]. Oedema is a drug class effect that precludes the use of the thiazolidinediones in patients with evidence of cardiac failure. The incidence of peripheral oedema was about 27% in one Australian study, which was reportedly somewhat higher than in other studies [31]. This was attributed to broader inclusion criteria or to the concurrent use of drugs such as non-steroidal anti-inflammatory drugs and calcium-channel blockers.

CYP2C8 is primarily responsible for the hydroxylation and N-demethylation of rosiglitazone in the human liver, with minor contributions from CYP2C9 [32]. By comparison, pioglitazone is oxidised by CYP2C8 and to a lesser extent by CYP3A4 [33]. The involvement of CYP3A4 in these pathways increases the potential for drug–drug interactions because this enzyme is involved in the metabolism of most drugs. CYP3A4 is also inducible by coadministered drugs including anti-epileptic agents and St John's wort. Thus, avoidance of potent CYP3A4 inducers in patients receiving thiazolidinediones is advisable.

The future role of thiazolidinediones is increasingly uncertain because of safety issues, which also include an increased risk of fracture and osteoporosis as well as exacerbation of diabetic macular oedema in some patients [28]. Predominantly because of concerns about myocardial ischaemia risk, the use of rosiglitazone has been suspended in the European Union and restricted in the US [34] and additional warnings have been added in other countries, including Australia [35]. Recently pioglitazone has been reported to be associated with an increased risk of bladder cancer in those with the longest cumulative exposure; a safety warning has been issued by the FDA [36] and its use has been suspended in some countries. An earlier agent, troglitazone, was discontinued in 2000 because of concerns of liver toxicity [37].

(c) Biguanides

The most serious potential adverse effect of the biguanide class of oral hypoglycaemic agents is lactic acidosis. Phenformin was withdrawn some years ago because of high risk of lactic acidosis. However, metformin is safer than phenformin, and the risk of developing lactic acidosis is low, at less then one in 10 000 patients prescribed the agent [28], providing the drug is not used in patients from high-risk groups. Metformin itself causes few adverse effects with gastrointestinal upset the most common.

Metformin does not undergo oxidative biotransformation and is excreted unchanged by the kidneys [38]. In normal renal function, metformin is unlikely to accumulate but is contraindicated in patients with risk factors for lactic acidosis or drug accumulation because of kidney, liver or cardiac dysfunction. Recently, it has been recognised in guidelines that metformin can be prescribed with vigilance, in people with stable chronic kidney disease down to an eGFR of 30 ml/min [28].

As per the product information, metformin may also lower serum vitamin B12 levels by reducing B12 absorption, and, while this vitamin is stored long term in the liver, it is prudent to assess the blood vitamin B12 level each couple of years to ensure it remains in the health range.

(d) Incretin mimetics

Subcutaneously administered exenatide is generally well tolerated. The most frequently reported adverse effect is nausea which leads to a discontinuation of treatment in about 2%–4% of patients although it usually improves with time [39]. The incidence of nausea is

higher during the initial weeks of treatment and declines thereafter. The observed weight loss in patients using exenatide is not associated with the occurrence of nausea. Other, usually minor and transient gastrointestinal complications such as vomiting and diarrhoea are also reported. Further adverse effects include feeling jittery, dizziness and headache [24, 39].

Severe hypoglycaemia causing unconsciousness, is rare in patients using exenatide. However, mild to moderate hypoglycaemia might occur more often with this agent, especially when used in combination with a sulphonylurea [24]. Similar to nausea, the incidence of hypoglycaemia peaks during the initiation of treatment and decreases over time.

Because exenatide delays gastric emptying, it can influence the efficacy of agents that require rapid gastrointestinal absorption. Therefore, medications that depend on threshold concentrations such as oral contraceptives and antibiotics should be administered at least one hour before exenatide.

Exenatide is administered by subcutaneous injection. The initial dosage should be 5 μg twice daily and if tolerated, should be increased to 10 μg twice daily after one month of treatment. Elimination of exenatide occurs mainly via glomerular filtration, hence the use of this agent is not recommended in patients with a severely impaired renal function.

(e) DPP-IV inhibitors

These agents are generally well tolerated. The most common side effects are upper respiratory tract infection and headache. Use is also associated with abdominal pain, nausea and diarrhoea. A key advantage is that this class do not cause hypoglycaemia at nearly the rate of the sulphonylureas, nor do they cause weight gain [24].

(f) Alpha-glucosidase inhibitors

Flatulence and diarrhoea are the main, very common side effects of this class of drugs which often limit their use [25].

(g) Insulin

The predominant adverse effects with insulin therapy are risk of hypoglycaemia and weight gain. One target of therapy in people requiring insulin treatment is that hypoglycaemia should be minimised. Mild hypoglycaemia occurs in ~30% of people at least once a year. Severe hypoglycaemia, which may be life-threatening, through causing trauma or triggering heart events such as myocardial infarct, occurs in 1%–2% yearly [28]. Occurrence of severe hypoglycaemia should be a ‘red flag’ to the diabetes healthcare team that the entire treatment approach needs revision, to identify the precipitating and predisposing factors and prevent recurrence.

Variations in genes that influence the pharmacodynamics of antidiabetic drugs

(a) Insulin secretagogues

There is considerable inter-individual variation in the response to these drugs. Several SUR1 variants have been identified including common polymorphisms in exon 16 and 18. It has been suggested that the Ser1369Ala variant of the ABCC8 gene that encodes SUR1 and also the Glu23Lys variant of Kir6.2 may be associated with the development of T2DM, especially if additional risk factors such as obesity are present [40].

(b) Insulin sensitisers

PPAR-gamma forms transcriptionally active heterodimers with RXR-beta so that defects in one or both genes may constitute an increased risk of insulin resistance. Thus, the common Pro12Ala variant of PPAR-gamma may contribute to the insulin resistant phenotype [41]. Obese individuals carrying the Ala-12 variant were at higher risk, especially if their dietary mono-unsaturated fatty acid intake was low. The observation that carriers of the RXR-beta C51T genotype who had a high body mass index also had an increased risk of gallstones may be relevant since both obesity and diabetes are important risk factors for gallstones [42]. Apart from possible contributions to disease development, as yet there is little information regarding the action of thiazolidinediones at variant PPAR-gamma.

(c) Biguanides

It now appears that AMPK is also a target for the biguanides. AMPK is a heterotrimeric complex containing a catalytic (alpha) subunit and two regulatory subunits (beta and gamma). In AMPK alpha2-null mice body weight and fat mass were increased and insulin sensitivity was impaired when they were administered a high-fat diet [43]. Single nucleotide polymorphisms in the AMPK alpha2 subunit gene were associated with altered serum lipoprotein concentrations in a patient cohort [44]. Similarly, relationships between diabetes and the –26C/T and IVS1+43C/T polymorphisms of the AMPK gamma2 subunit gene were evaluated. Patients who were homozygous for the –26T allele were associated with a higher risk of developing T2DM and patients who carried the IVS1+43TT variant had higher serum concentrations of triglycerides and cholesterol [45]. To date, information on the role of AMPK beta-subunit gene variation and disease development have not been delineated. Moreover, how AMPK subunit polymorphisms influence metformin efficacy in T2DM is yet to be established.

(d) and (e) Incretin mimetics and DPP-IV inhibitors

A single nucleotide polymorphism in the GLP-1 gene that encodes the major GLP-1 receptor variant, in which threonine 149 is replaced by methionine, is activated differentially by GLP-1 *in vitro* [46]. This receptor variant could account, in part, for different responses to GLP-1 agonists such as exenatide, but this possibility has not yet been actively explored.

With the exception of saxagliptin the available DPP-IV agents are not CYP substrates and so are seldom associated with pharmacokinetic drug-drug interactions. Vildagliptin has a

half-life of 2.8 hours and generates several metabolites by CYP-independent pathways [47], whereas the mean apparent half-life for plasma sitagliptin is 9–14 hours [48]. In contrast, saxagliptin is oxidised by CYPs 3A4 and 3A5 to a major metabolite that is pharmacologically active. Instead, renal excretion is the most important elimination pathway for the drugs. It has been established that dose adjustments are recommended for patients with renal impairment.

Management of type 2 diabetes in adolescents

The principles of T2DM therapy in adolescents are similar to those in adults, although a much more limited range of pharmacological agents are approved and used. Again, lifestyle modification including nutritional components, physical activity and weight loss are first-line management tools [4]. However, in many instances, these are insufficient to meet treatment goals and the addition of pharmacotherapy is needed. In most countries, insulin and metformin are the only drugs approved for use in children and adolescents. Sulphonylurea agents are approved in fewer countries, but other agents have generally not yet had adequate appraisal of safety and efficacy in children and adolescents, and are not approved. The treatment options for T2DM in Adolescents and Youth (TODAY) study [49] is a randomised trial evaluating three arms of pharmacological intervention for T2DM in newly diagnosed T2DM adolescents. It compares the efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention. However, as described earlier, there is increasing concern about emerging serious adverse effects of the thiazolidinediones in any age group and it is unlikely they will have a significant future role. In any case, their known class effect to cause weight gain [50] has always been a disincentive to their use in adolescents.

The choice of initial therapy in T2DM in adolescents depends on the clinical presentation including symptoms, severity of hyperglycaemia and presence or absence of diabetic ketoacidosis. The differentiation of type 1 from type 2 diabetes is not always clear at presentation in adolescents and T2DM can present with ketosis (up to 33%) or ketoacidosis (5%–25%) [51]. In those with severe hyperglycaemia and/or ketosis/ketoacidosis, initial treatment should always be with insulin for initial stabilisation and rapid metabolic control, in conjunction with lifestyle measures. Laboratory investigations (particularly type 1 diabetes related antibodies and C-peptide) and clinical course will help clarify the diagnosis and it is common practice to add metformin and wean insulin to the point of cessation if possible. Asymptomatic patients will usually have a trial of lifestyle modification without drug therapy, while those with mild-to-moderate symptoms without ketosis will usually be treated with metformin in addition to lifestyle modification [52, 53]. The adequacy of ongoing therapy is judged by a number of clinical criteria, but mainly HbA1c <7% and fasting plasma glucose <7 mmol/l.

The proportion of adolescents with T2DM treated with lifestyle modification alone is reported to be 11%–50% [53]. However, as in adults, failure of therapy increases with duration. When lifestyle modification alone is inadequate, metformin is commonly added. Surveys indicate that a substantial proportion of adolescents with T2DM take metformin

(28%–71%) [53]. Metformin is approved by the FDA and also recommended by the American Diabetes Association and the International Society for Paediatric and Adolescent Diabetes as the first-line pharmacological agent in adolescents with T2DM. Doses up to a maximum of 2000 mg per day are usually recommended [53], divided twice daily, although the whole dose can be taken once a day using an extended release preparation which may improve gastrointestinal tolerability and compliance [54]. Metformin is also used as an adjunct to therapy in type 1 diabetes in adolescents with significant insulin resistance. A recent systematic review [55] (including adults and adolescents) demonstrated reduced insulin requirement with metformin, but no improved metabolic outcome and no data on cardiovascular outcomes are available.

When lifestyles measures and metformin are inadequate, or metformin is not tolerated or is contraindicated, insulin is added or substituted. Randomised controlled trials (RCT) comparing various insulin regimens in T2DM in adolescents do not exist, however data from adult experience are generally applicable. A bedtime long-acting insulin analogue is commonly used as initial insulin therapy, but a wide range of other regimens are used according to local preference, including multiple daily injections. Some guidelines in adults [56] suggest that isophane insulin should be used first and insulin analogues reserved for special indications. However there are some data to suggest lower rates of hypoglycaemia with analogues [57] and they are favoured as first-line insulin therapy by paediatric endocrinologists [53]. At present, insulin pump therapy is generally not recommended in T2DM [58, 59]. This is largely due to the increased intensity and cost of therapy, and because targets can often be met with simpler insulin therapy. However lower rates of hypoglycaemia and increased sensitivity to insulin when delivered by pump are attractive potential benefits.

Drugs other than metformin or insulin for adolescents with T2DM are not approved by regulatory authorities, although surveys indicate significant usage by some providers [53]. Newer agents such as GLP1 agonists and DPP4 inhibitors [50] may play a future role, especially in more difficult clinical situations.

Management of obesity in adolescents

Lifestyle intervention through exercise and dietary modification should be the primary treatment for obesity in children and adolescents; drug therapy should be considered a secondary option in refractory situations and usually only in adolescents. Family-targeted behavioural and lifestyle intervention programs have been shown to have clinically significant benefits [16], although these benefits are not always sustained. Drug therapy used as an adjunct to lifestyle intervention in adolescents with obesity was analysed in a recent Cochrane review, including sibutramine, orlistat and metformin [16]. The use of sibutramine (a serotonin and noradrenaline reuptake inhibitor) in adolescents was examined in five studies, with data showing improved BMI over lifestyle alone; adverse events were greater in sibutramine than placebo-treated adolescents, but with low rates of any serious adverse events. Subsequently, however, sibutramine has been withdrawn from most parts of the world, including the US, Europe and Australia because of post-

marketing surveillance data which indicated increased risk of myocardial infarction and stroke in patients with existing cardiovascular disease [60]. In two available RCTs of orlistat (a gastrointestinal lipase inhibitor) in combination with lifestyle measures in adolescents there was also a greater improvement in BMI over placebo; however orlistat-treated patients had a much higher prevalence of gastrointestinal adverse effects, particularly oily stool evacuation, cramps, abdominal pain and increased defaecation, but also increased asymptomatic gallstones in one study [61]. While orlistat is still available, in May 2010 the FDA warned about a possible link with severe liver injury in rare cases [62], and labelling was revised to include this.

The most relevant drug used as an adjunct to lifestyle measures in adolescents with obesity is metformin, a biguanide oral hypoglycaemic agent. There are now several studies indicating its safety and efficacy in adolescents with insulin resistance and obesity (or prediabetes). In a recent systematic review and meta-analysis that included five suitable RCTs [63], metformin was concluded to have moderate efficacy in reducing BMI and insulin in hyperinsulinaemic obese children and adolescents, although no long-term studies were available. In pooled analysis, metformin reduced BMI by a mean 1.42 mg/m^2 which was considered moderate compared to available data on subitramine (–1.66 kg/m^2) or orlistat (–0.76 kg/m^2) [16]. Gastrointestinal adverse events were more frequently reported in those receiving metformin (risk difference 10%–14%), but there were no serious adverse events. There is a need to further evaluate metformin in longer-term studies as an adjunct to more intensive lifestyle interventions [64]. Even without this further evidence, metformin is commonly used in clinical practice in adolescents with obesity, insulin resistance and other features of metabolic syndrome because of its favourable safety profile and its established use as pharmacotherapy in T2DM in adolescents.

Management of obesity in adults and commercial programs in Australia

There is a wide range of weight-loss programs available including commercial weight-loss programs provided in the pharmacy as well as Jenny Craig and Weight Watchers, internet-based programs, weight-loss products such as meal replacements available from supermarkets, and community-based weight-management or exercise programs. The Weight Management Council of Australia provides a voluntary code of practice for commercial weight-loss companies [65]. Although commercial weight-loss programs are very popular, they usually only induce large short-term changes in weight and these changes are mostly transient. There is a need to establish evidence-based practices that demonstrate efficacy, safety and long-term weight maintenance. At this point in time there is very little data on the efficacy or outcomes of the commercial weight-loss programs in Australia [75].

Various factors affect an individual's efforts in terms of short-term weight loss and maintenance [66]. The majority of overweight adults have a history of previous weight-loss treatments. A study by Burke et al. (2008) examined individuals' past experiences with weight-loss treatments [67]. Program features identified as least satisfying included dissatisfaction with diet product (20.4%) and concerns about safety of program or product

(17.2%). The most common reasons for difficulty in successfully losing weight that were identified were difficulty to make and maintain lifestyle change (38%), no time (32.4%) and lack of support (18.5%). Similarly, a study by Jeffery et al. (2004) examined how individuals' attitudes about weight-loss efforts change during weight loss [68]. Individuals who lost less weight during the six months reported feeling more negative reactions. Reported satisfaction in relation to weight-loss effort declined over time, and in the last two months, perceived benefits were approximately equal to perceived costs of weight change.

Various studies have shown that superior weight loss occurs when cognitive behavioural therapy is added to diet and exercise interventions. Health education is required to facilitate patients making informed choices about their health. A study by Swift et al. (2009) showed that intended weight loss and outcomes were positively associated with health beliefs [69]. The results of this study also suggest that healthcare professionals may find it productive to discuss the social and aesthetic benefits associated with weight management. Cognitive strategies that have been identified in weight management include increasing awareness of negative thoughts, problemsolving alternatives to negative self-talk and pre-intervention strategies such as motivational interviewing and establishing objective weight-loss outcomes [70]. Establishing readiness for change via motivational interviewing has been shown to predict sustained change efforts in physical exercise, dietary change and adherence [70].

In all of these programs there is a need to clarify patients' expectations for weight-loss outcomes, provide objective and realistic goals, and re-evaluate these goals over the course of management.

Management of type 2 diabetes and obesity in the health system

There are a variety of effective therapies available and new approaches to be trialled in future. Notwithstanding the availability of effective therapies and treatment guidelines, translation of evidence into practice and delivering optimal care represents a significant challenge to healthcare systems. Because of the nature of T2DM and the need for patients to understand and take control of their lifestyle in order to reduce their health risk, people with T2DM are especially vulnerable and need intensive chronic disease management and ongoing support. From a systems perspective, however, limited patient access to diabetes healthcare professionals, as a result of personnel shortages [71], especially in rural and remote areas, and lack of systems to support chronic disease management with continuity of care [72, 73], are well recognised barriers to achieving optimal health outcomes for diabetes. Hence, there is a need to develop cost-effective innovative models of diabetes and weight management care based on more intensive continuity of care [74] including self-management support, regular monitoring and follow-up in order to enable patients to achieve the recommended targets.

Pharmacists in type 2 diabetes care

In recent years, pharmacists, as highly trained healthcare professionals with expertise in medicines, have sought to develop an expanded role in diabetes care to meet the burgeoning needs of this growing patient population. There are compelling arguments which support

this expanded involvement. Community pharmacies provide an established and visible network, extending to remote areas, of easily accessible healthcare professionals. Through regular and less formal contact than that with doctors, pharmacists are able to build strong relationships with patients and become a reliable source of information. Pharmacists can also have ongoing relationships with other healthcare providers and can serve as the 'bridge' between healthcare providers and the patients, thus ensuring continuity of care. Therefore visits to the community pharmacy offer an excellent opportunity to screen at-risk patients and to provide education and support to diagnosed T2DM patients, particularly if they do not regularly visit a general practitioner (GP) or diabetes educator. In addition, as medications play a key role in preventing the complications of T2DM, ensuring their effectiveness through monitoring and adherence support as well as screening for drug -related problems, is critical to achieving improved health outcomes.

Specific services that pharmacists have offered patients in T2DM include opportunistic screening for undiagnosed disease [76], diabetes self-management education, medication-adherence support and medication management such as the at-home medicines review, ensuring the quality and evidence-based use of medications, monitoring clinical outcome measures eg blood glucose levels, blood pressure, lipid levels, and reminding patients of the importance of regular examinations for diabetic complications [77].

Two recent systematic reviews of the effects of these pharmacist–outpatient interventions on adults with diabetes mellitus showed significant improvements in HbA1C for patients in a diverse group of clinical settings and countries. Overall, the results suggest that pharmacist interventions can reduce long-term costs by improving glycaemic control and thus diminishing future diabetes complications [78, 79].

Diabetes care in Australian pharmacy

In 1999, a specialised T2DM service, the Diabetes Medication Assistance Service (DMAS), was developed for delivery in Australian community pharmacy. Its focus was on the provision of self-management support through a series of regular visits with a credentialed pharmacist to assist people with T2DM more effectively self-manage their condition and improve their use of medicines. At each visit, the pharmacist tailored the consultation to the individual needs of the patient. By using motivational interviewing and goal setting, in combination with education, the pharmacist aimed to empower the patient to take better control of their diabetes [80].

A systematic program of research involving two pilot studies, an RCT and an implementation trial has provided a strong evidence base for the clinical efficacy and cost-effectiveness of the DMAS. The RCT used a multi-site, control versus intervention, repeated measures design within five states in Australia. Fifty-six community pharmacies, 28 interventions and 28 controls, were randomly selected from a representative sample of urban and rural areas. Intervention pharmacies delivered the DMAS to patients with T2DM during the course of five visits to the pharmacy over a period of six months. Control pharmacists assessed patients at birth and six months and delivered no intervention. A total of 289 patients (149 interventions and 140 controls) completed the study. Significantly greater

improvements in glycaemic control were seen in the intervention group compared to the control, ie a mean reduction in HbA1c of –0.97% (95% CI: –0.8, –1.14) in the intervention group compared with –0.27% (95% CI: –0.15, –0.39) in the control group. Improvements were also seen in blood pressure control and quality of life in the intervention group. Pharmacists identified a range of interventions (4309 for 149 patients) to improve the care and wellbeing of their patients. Monitoring of the progress of the disease and as well as the outcomes of the interventions appeared to be the essential element of the disease state management process. Both pharmacists and patients identified the outstanding benefits of the service and expressed great satisfaction with service provision. The DMAS was shown to be cost-effective when compared to other government funded programs [75].

The RCT was followed by a national implementation trial, the Diabetes Pilot Program (DPP) which aimed to answer three further questions regarding the DMAS service: 1) what are the key barriers and facilitators to national implementation of the DMAS service 2) what is the optimal number of pharmacy visits and 3) what is the sustainability of clinical improvements beyond DMAS service delivery. A national quota sample of 90 community pharmacies in Australia were randomly assigned into Group 1 (six-month DMAS) or Group 2 (12-month DMAS) and subsequently recruited a total of 524 patients. The implementation process was carefully tracked with data collected through individual or group interviews with 100 patients, 28 pharmacists and 41 GPs at the beginning and at the end of DMAS to explore their experiences and perceptions of DMAS and to identify barriers and facilitators. A wide range of clinical (HbA1c, blood pressure, lipids) and quality of life outcome measures were assessed.

The results indicated that the DMAS may be successfully implemented in diverse community pharmacy settings providing: 1) the pharmacy has adequate staff and infrastructure; 2) there are good pharmacist-GP relationships; 3) the pharmacy has a pool of eligible patients; 4) there is effective promotion and integration of the DMAS within the healthcare sector; and 5) there is adequate remuneration for service delivery. The clinical outcomes of the implementation trial mirrored those of the RCT. Both the six-month and 12-month DMAS resulted in significant and similar reductions in HbA1c (–0.9; 95% CI:–0.65, –1.12), total cholesterol (–0.3; 95% CI:–0.07, –0.38), triglycerides (–0.3; 95% CI:–0.10, –0.53) and overall ten year CVD risk; moreover the benefits were sustained up to 12 months after the end of the DMAS [81]. The extent and sustainability of clinical improvements achieved by the DMAS together with the resulting reduction in cardiovascular risk should translate into future cost savings to healthcare systems by delaying and reducing diabetes related complications. Collectively these studies support the feasibility and efficacy of community pharmacy T2DM diabetes care in the Australian healthcare setting.

In addition to the effectiveness of pharmacy support for people with T2DM, several studies have also supported the feasibility and efficacy of opportunistic screening for T2DM in community pharmacy [82–84]. Community pharmacy provides a logical site with its established, expansive and visible network of easily accessible health professionals, able to access a broad population who are apparently healthy and who rarely come into contact with GPs or nurses.

Weight-management programs in community pharmacy

In the context of weight management in the UK, the government recognised the contribution that pharmacy can make in managing the obesity epidemic in the white paper *Pharmacy in England* [85]. In doing so, pharmacy contract negotiators recommended a government-funded national weight-management service initiative in community pharmacies [86].

Several other studies have illustrated that community pharmacists' involvement in weight-loss programs has been associated with successful weight loss. A study in Denmark reported the results of 'slimming courses' held at 19 community pharmacies for 269 obese patients [87]. Average weight loss was 5.3 kg for females and 6.2 kg for males. At one year follow-up 20% of the patients who had completed the course had maintained a weight loss of greater than five kilograms [87]. Community pharmacists could play a key role in providing holistic weight-loss programs and collaborating with healthcare professionals, rather than being seen as product suppliers [88].

A recent Pharmacy Pulse survey showed that more than 17% of pharmacies in Australia want to be known as a destination for a weight-loss solution [89]. In 2003, the National Pharmacy Database Project reported that 8.7% of 1131 Australian community pharmacies surveyed conducted weight-management programs by trained staff [90]. At present, the majority of commercial weight-loss programs are based on very low-calorie diets that are mostly achieved by meal replacement shakes and soups. Other factors necessary for weight change such as increased physical activity are supplementary to the weight-loss product and used to augment the product specifically. Most programs provide ongoing support either by in-store consultants, a website or telephone support services.

Lifeweight™ was the first nationally released weight-management program specifically designed for community pharmacy. The program combines the product Xenical® (orlistat) with pharmacist-delivered cognitive services to provide a holistic package [75].

It was launched in 2004, following the decision to down schedule Xenical® (orlistat) from a prescription to pharmacist-only medication. The program was developed in collaboration with the Pharmacy Guild of Australia, the Pharmaceutical Society of Australia, the Australian Institute of Pharmacy Management and Roche, the manufacturers of Xenical®. Training programs and resources were made available for pharmacists and pharmacy assistants to increase their skills in delivering the program. Content of the program is comprehensive and well structured, based on evidence-based material and is aligned with National Health and Medical Research Council guidelines [75]. Baseline and longitudinal patient data is collected including age, weight, body mass index, target weight, measured progress to target, final weight on completion of or withdrawal from the program. Adoption and uptake of Lifeweight™ in community pharmacies has declined in recent times, as both consumers and pharmacists have articulated a need for a well-planned, accredited, community pharmacy-based, remunerated service that would deliver a more comprehensive collaborative service [91]. Such a service would ideally not be based on a product but a wholistic, evidence-based program. This would allow for increased numbers of overweight and obese Australians to have access to a consistent, evidence-based, integrated

healthcare weight-management program. Improvement in health for the overweight and obese, and better management of diabetes, hypertension, hypercholesterolemia and other obesity-related health issues would be the outcome. This would result in decreased costs to the healthcare system due to reduced mortality and morbidity attributed to the overweight and obese Australian population.

Conclusion

Innovation of service delivery is critical to address the burgeoning problems of T2DM, obesity and related diseases. The complications of these diseases place a considerable burden on the healthcare system.

The review of available pharmacotherapy for T2DM and obesity shows that there is considerable inter-individual variation in response to the various drug classes and the reasons for this are currently under investigation. In adolescents and children the approach to therapy is not merely a reflection of recommendations for adults. In terms of support for pharmacotherapy and lifestyle interventions, community pharmacy programs have provided evidence of effectiveness in T2DM, however at this point in time support for weight-loss programs has been inhibited by the focus on individual commercial products. Nevertheless, community pharmacists are a valuable resource of trained healthcare professionals that should be utilised to provide diabetes and obesity prevention and care services as part of an integrated primary care sector approach.

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