Prescribing for people with diabesity: Issue of polypharmacy

Victoria Ruszala

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Article points

1. Polypharmacy is the use of at least four different medicines by an individual, and people with type 2 diabetes and obesity are susceptible to being prescribed multiple medicines.
2. Many of the consequences of polypharmacy can lead to further medicines prescriptions.
3. Improving patient adherence and the patient–practitioner relationship are crucial in creating drug regimens that minimises polypharmacy.

Key words

– Adherence/non-adherence
– Complex drug interactions
– Polypharmacy

Author

Victoria Ruszala is Highly Specialist Pharmacist in Diabetes at North Bristol NHS Trust, Bristol.

There is a range of potential medicines to manage type 2 diabetes and, with a drive to meet clinical targets in glycaemia, blood pressure and lipid levels, polypharmacy is becoming common practice. This article covers the factors contributing to polypharmacy (prescribing a minimum of four medicines), the consequences for practitioner and the individual with diabesity, and the strategies to improve patient adherence among this population.

Type 2 diabetes is a condition that demands attention. In total, 9.6 million people in England are at high risk of developing type 2 diabetes, and this number is rising year on year (Diabetes UK, 2015). With this growing population, it has become an expensive condition to manage. In the NHS alone, £10 billion a year is spent on diabetes, which is 10% of the annual NHS budget. Of this, £7.7 billion is spent on managing and treating diabetes-related complications (Hex et al, 2012). The biggest spend, £3000 million, was on diabetes-related cardiovascular disease in 2010/11 (Diabetes UK, 2014). With the cost pressures facing the NHS, there is a drive to prevent diabetes-related comorbidities and improve health outcomes to ultimately reduce morbidity.

Type 2 diabetes is a complex disease, even when first diagnosed. Due to its slow onset, diagnosed individuals may present with a range of comorbidities on day one, and then present with associated complications shortly afterwards. Diabesity is a term coined fairly recently, but the link between diabetes and obesity was first noted in 1973 by Ethan Sims. Participants in his study population were overfed for 6 months and presented with a range of metabolic disturbances including increased insulin production (and resistance), hypertension, hyperglycaemia and hyperlipidaemia (Sims et al, 1973). Our understanding of the interplay between these factors has increased over the years with results from trials including the UKPDS (United Kingdom Prospective Diabetes Study) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) all showing that the control of these factors leads to long-term prevention of cardiovascular disease and other diabetes-associated complications, such as retinopathy and nephropathy (UKPDS Group, 1998a; 1998b; Patel et al, 2008; Duckworth et al, 2009; Ismail-Beigi et al, 2010). Therefore, in order to achieve the best outcomes for individuals with diabesity, we must continually strive to "treat" all aspects of the condition.

Available therapies for type 2 diabetes

Diabetes is an attractive area for pharmaceutical companies – there is a range of physiological targets to be investigated and there remains unmet need. There are currently nine drug classes acting on different pathways available for prescription in the UK (biguanides [i.e. metformin], sulphonylureas, meglitinides, alpha-glucosidase inhibitors, glitazones, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium–glucose cotransporter 2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists and insulins) and, as a result, a person with type 2 diabetes and the professional caring for them are faced with a raft of varied treatment options.

This is no bad thing as it means that

individually tailored therapy is becoming more of a reality with each passing year. However, for the clinician, it can be confusing deciding which drug has the best evidence and is likely to achieve the best outcome, and for the individual, it can mean a lifetime facing a large volume of drugs and the associated complexities.

Causes of polypharmacy

Polypharmacy is the use of at least four different medicines by an individual, and people with type 2 diabetes and obesity are susceptible to being prescribed multiple medicines. As a result, this population must be routinely and frequently assessed to determine if their medicines are serving a purpose and are still effective. The temptation to add another drug if treatment does not appear to be effective is embedded in our health system psychology. This and other factors including those listed below can contribute to polypharmacy (Austin, 2006):

- Multiple prescribers
- Complex drug therapies as a result of multiple comorbidities
- Adverse drug reactions that may be interpreted as new medical conditions (e.g. weight gain)
- An aging population
- Psychosocial contributions.

Polypharmacy specifics: People with diabesity

Multiple prescribers

Poor communication between primary and secondary care providers can contribute and lead to problems with polypharmacy among people with diabesity. In general, people with diabesity are expected to receive the majority of their care and treatment in primary care, although as the complexity of diabetes increases, they are likely to be periodically seen by specialists who are focussed on one main aspect of care. Primary care practitioners are expected to understand and enact the recommendations of individual specialists, while also continuing to monitor the efficacy of treatments and the achievement of clinical targets.

In addition, secondary care practitioners rely on patients to inform them of changes that may have occurred since their last review, and they rely on primary care practitioners to know what information is essential in a referral. It is, therefore, very easy to see where gaps in information can occur and lead to complex drug regimens that are only partially understood by each prescriber. In this situation, medicines are susceptible to being used incorrectly or ineffectively. This can lead to the introduction of further medicines, with the aim of improving symptoms and meeting targets.

Complex drug therapies as a result of multiple comorbidities

NICE has set targets for glycaemic, blood pressure and lipid levels for people with type 2 diabetes that offer the best opportunity to prevent cardiovascular complications, and it recommends a range of therapies that can help to achieve this (NICE, 2009a). There are currently nine classes of medications available for glycaemic control (including insulin), eight for hypertension and four for lipid control. All have evidence of different degrees of benefit and most are recommended in national and international guidance as options to meet the outlined targets (NICE 2009a; Ryden et al, 2013; American Diabetes Association, 2014).

Some therapies are recommended more strongly than others, and, among the diabese population, you would expect to see at least metformin, an angiotensin-converting-enzyme (ACE) inhibitor and a statin being prescribed due to the increased cardiovascular risk. However, if this trio of medicines alone is unsuccessful, the recommendations become broader and the treatment options more variable. The overriding message to clinicians is "achieve the target in any way possible for the best possible outcome". This results in a situation where, if targets are not being met, the individual with diabesity may have more medications added during each medical review. This is also true if further complications develop, such as kidney disease or neuropathy.

The American Diabetes Association (2014) also recommends assessment for concurrent conditions such as heart failure, depression and anxiety, and other conditions that are found to

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2. Poor communication between primary and secondary care providers can contribute and lead to problems with polypharmacy.

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1. As well as increasing the risk of adverse drug reactions, increasing the number of prescribed drugs itself contributes to polypharmacy, as yet more medication may be prescribed to treat the initial adverse side-effects.
2. Weight gain can be a adverse drug reaction caused by insulin and many of the oral drug options for type 2 diabetes.
3. Assessment of the causes and consequences of polypharmacy relies on an honest relationship between the practitioner and the patient and a degree of empathy on both sides.

occur at higher rates among people with diabetes than among an age-matched population without diabetes. Although focussed particularly on older people with diabetes, an article in *The Journal of the American Medical Association* by Boyd et al (2005) found that, if all guidelines were followed for a patient with multiple comorbidities, they would be prescribed on average 12 different medications. Extensive polypharmacy can lead to complex drug regimens of different formulations and multiple frequencies, which may result in reduced patient adherence. Patient non-adherence can exacerbate the problems associated with polypharmacy and lead to further prescribing. Adherence will be discussed later in this article.

Adverse drug reactions

Increasing the number of prescribed drugs increases the chance of adverse drug reactions or adverse drug–drug interactions (Tinett et al, 2004). It has been shown that only four medications are needed to cause an adverse drug reaction (Jacubeit et al, 1990) – so, if up to 12 medications are being prescribed, this becomes an almost certainty.

Increasing the number of prescribed drugs itself contributes to polypharmacy, as yet more medication may be prescribed to treat the initial adverse side effects. It is difficult to determine what drug may cause an adverse drug reaction and determining the culprit relies heavily on an accurate history from the patient. This is where it is crucial to be able to communicate with the patient honestly and openly. If they feel that a particular medication has caused an adverse effect, they are far more likely to be non-adherent to that aspect of treatment. This can lead to further prescribing when medicines are deemed "ineffective" when, in fact, they are not being taken at all. An honest and open relationship between practitioner and patient is therefore crucial.

Weight Gain

Weight reduction has been shown to be the most beneficial intervention for both type 2 diabetes and obesity. It is associated with decreased insulin resistance, lower blood pressure and lower triglyceride levels (Mitri and Hamdy, 2009). Unfortunately, many of the recommended treatment options that can efficiently lower HbA_{1c} can cause significant weight gain (insulins, sulphonylureas and thiazolidinediones). This is likely to reduce patient acceptability of the regimen and requires careful consideration and discussion with the patient. Metformin, DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors have been shown to be more favourable in weight management and should be considered positively in this population (Mitri and Hamdy, 2009). However, this must be balanced by treatment recommendations from local and national bodies, costs and prescriber experience, especially with the very new classes of medications.

Consequences of polypharmacy

Understanding the consequences of polypharmacy (*Box 1*) is equally as important as understanding the causes, as the consequences can often lead to further prescribing.

Assessment of the causes and consequences relies on an honest relationship between the practitioner and the patient and a degree of empathy on both sides – a concordant approach (see *Box 2*). A concordant approach taken by the clinician ensures the patient knows their views are respected and, therefore, can discuss any subsequent difficulties in a bid to optimise their drug regimen.

Box 1. Consequences of polypharmacy (from Austin, 2006).

- Adverse drug events and drug–drug interactions
- Decreased patient adherence to the drug regimen
- Potential duplication of therapy
- Decreased quality of life
- Increased costs
- Emergency department visits, hospitalisations, additional medical or surgical interventions

Patient adherence

"Drugs don't work in patients who don't take them." C. Everett Koop, M.D.

Non-adherence is a problem regularly met by

Box 2. Concordance, compliance and adherence.

- Concordance is a term related to the process of the consultation in which prescribing occurs based on a partnership between patient and clinician. It is defined as "agreement between the patient and healthcare professional, reached after negotiation that respects the beliefs and wishes of the patient in determining whether, when and how their medicine is taken, and (in which) the primacy of the patient's decision (is recognized)" (Marinker et al, 1997).
- Compliance is defined as "the extent to which the patient follows the healthcare professionals' advice and takes the treatment" (Cushing and Metcalfe, 2007). This assumes the patient to be passive and obedient, following the approach outlined by the doctor with minimal decision-making or input from the patient. This model is now viewed as outdated.
- Adherence is a term that is now often used instead of compliance. The World Health Organization defines adherence as "…the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health-care provider" (Sabate, 2003).

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1. Patient adherence is an important concept when considering strategies to improve health behaviours.
2. Although adherence can be improved, no single intervention will work for all individuals, and so strategies should be tailored to the individual and their personal difficulties.

health practitioners, and is particularly prevalent among individuals with chronic conditions. Estimates of adherence to diabetes medication is between 50–60%, with even less adherence to diet and lifestyle changes (Delamater, 2006). A number of studies have investigated the reasons for non-adherence and the populations most likely to be non-adherent. In 2003, the World Health Organization (WHO) published an in-depth review of adherence, including disease-specific reviews of long-term conditions (Sabate, 2003). Although over 10-years old, this report is still valuable as it assessed adherence to different aspects of diabetes treatment separately (blood glucose monitoring, diet, administration of medications and physical activity). The report found that there was variation in adherence to the different treatment components and a very wide range of variables affecting adherence behaviours (e.g. treatment and disease characteristics; intra-personal factors; inter-personal factors; and environmental factors). The report did not assume or find that the rate of non-adherence was similar for each component; this is important to remember when faced with a patient who is believed to be non-adherent.

It is important to note that it is very difficult to truly measure adherence, but there are multiple methodologies available (direct or indirect methods [see *Box 3*]).

An assumption by healthcare practitioners that a patient is non-adherent or just "not interested" can damage the relationship with the patient, so it is important to find the cause of the disengagement. More concerning is the perception of poorer adherence associated with obese individuals. It has been found that obese patients are perceived to be more non-adherent by doctors than non-obese individuals (Huizinga et al, 2010). This stigma can further weaken the relationship and result in poorer outcomes among obese individuals compared to non-obese counterparts.

Strategies to improve adherence

Where non-adherence has been identified it is important to address the issues and identify strategies to improve behaviour. NICE recognises that non-adherence is common and that most patients are non-adherent at some point during treatment. In response to this, NICE issued a guideline to support prescribers in developing a relationship with patients, which enables patients to make informed choices about their prescribed medicines (NICE, 2009b). Although adherence can be improved, no single intervention will work for all individuals, and so strategies should be tailored to the individual and their own personal difficulties.

Osterberg and Blaschke (2005) identify potential strategies for dealing with different aspects of non-adherence. These can be incorporated into diabetes care reviews with people with diabesity:

- Firstly, identify poor adherence:
  - Look for markers: missed appointments, lack of response to medication.
  - Ask about barriers to adherence without

Box 3. Measuring patient adherence.

Direct methods include directly observed therapy and measurements of the level of medicine and biological markers in the blood.

Indirect methods include patient questionnaires, self-reports, pill counts, rate of prescription refills, measurement of physiological markers and patient diaries.

Direct methods are considered to be more robust than indirect methods, but both have limitations and no particular method is considered the gold standard. Although certain methods of measuring adherence may be preferred in specific clinical or research settings, a combination of measures maximises accuracy (Osterberg and Blaschke, 2005; Ho et al, 2009).

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1. NICE recommends in clinical guideline 76 that at every consultation the patient's knowledge, understanding and concerns about their medicines should be reviewed.
2. Multiple drug therapy has become the standard of care in the treatment of type 2 diabetes.

being confrontational.

- Reinforce desirable behaviour and results when appropriate (such as positive changes in diet, weight, blood pressure, lipids, HbA_{1c} and self-monitoring).
- Explain treatment decisions and emphasise the value of the regimen (e.g. prevention of long-term complications, lack of hyperglycaemic symptoms).
- Allow the individual to set personal goals for treatment and elicit their feelings about their ability to follow the regimen:
  - Listen to the patient, these goals can be adjusted with each review and be customised in accordance with their wishes and changes in their circumstances.
- Simplify the regimen as much as possible, for example:
  - Once- or twice-daily dosing (twice-daily metformin rather than thrice-daily; once-daily DPP-4 inhibitors).
  - Extended-release medications (weekly GLP-1 analogues).
  - Combination tablets (after appropriate dose titration).

The 2003 WHO report also showed that the complexity of the treatment regimen has an effect on adherence, while the use of single-dose formulations and simpler regimens improved adherence in those who had previously demonstrated non-adherence.

NICE recommends that at every consultation the patient's knowledge, understanding and concerns about their medicines should be reviewed. The patient should also be asked about their views on the need for the medicine, and should be offered repeat information and reviews at suitable intervals, especially with complex medication regimens (NICE, 2009b).

A focus of these appointments should be to develop a collaborative relationship between the patient and the practitioner. However, diabetes is essentially a self-managed condition and, therefore, requires patients to have a degree of autonomy and motivation to enable success. Emphasis should be given to self-treatment, development of personal responsibility and self-empowerment, which is often not a simple task. Developing the patient-centred care model and enabling ownership has been shown to be a successful strategy to improve adherence to medication regimens and ultimately improve long-term outcomes (Laxy et al, 2014).

Although enabling patients to be part of prescribing decisions is important, the healthcare practitioner should still offer their opinion and structure the consultation. Evidence-based practice acknowledges and incorporates the influence of the patient in decision-making (Knight, 2013). However, clinical expertise enables the prescriber to explore the common ground between the best evidence and the patient's values and sometimes influence the patient towards a particular treatment if required.

Pharmacists are essential members of the multi-disciplinary team, especially when tackling medication non-adherence. Pharmacist interventions involving education and counselling have led to improved adherence in type 2 diabetes (Omran et al, 2012; Antoine et al, 2014). There is not enough evidence available at present to establish the effects on health outcomes, although some studies have shown significant improvement in glycaemic control. Both primary and secondary care pharmacists have a role to play in improving adherence, especially when patients move between care facilities when it is likely medications or doses have been changed and counselling can provide support.

Conclusion

Multiple drug therapy has become the standard of care in the treatment of type 2 diabetes. However, complex drug regimens need regular review and evaluation by healthcare practitioners to ensure that unnecessary and redundant medications are discontinued and alternatives are available which better suit a patient's lifestyle.

Monitoring prescribed drugs that cause weight-gain or drug interactions should be a part of every consultation as this will benefit not only obesity but overall diabetes management. People with diabesity and healthcare professionals need to work together to develop an active relationship that encourages shared goals of therapy and

addresses concerns about adherence. Achieving an individualised and realistic therapeutic plan is key to ensuring effective healthcare. ■

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