RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

PS04/19

# Position statement on antidepressants and depression

May 2019

POSITION STATEMENT

# Antidepressants and depression

## The College position

Depression is a condition that can affect people differently and cause a wide variety of distressing symptoms. It can lead to relationship and family breakdown, increase the likelihood of drug or alcohol addiction, reduce the ability to overcome serious illness and increase mortality rates – not just from the risk of suicide. Depending on its severity, clinicians can offer a range of different treatments that can often significantly improve the lives of patients.

For adults affected by moderate to severe depression, where there is a clear detrimental impact on their everyday function and quality of life, the College recognises the following:

- The use of evidence-based psychological treatments is recommended for initial treatment (NICE, 2009). When an individual does not respond to, or engage with, initial treatment or has more severe depressive symptoms, antidepressants are a recommended therapeutic option.

- The routine use of antidepressants for mild and sub-threshold depressive symptoms among adults is not generally recommended. However, prescription may be considered when clinically indicated (i.e. patients with a history of moderate or severe depression; initial presentation of subthreshold depressive symptoms that have been present for a long period, typically at least 2 years; subthreshold depressive symptoms or mild depression that persist(s) after other interventions) (NICE, 2009).

- Antidepressant use among children and adolescents should only be part of second-line treatment for moderate to severe depression when patients are unresponsive to psychological therapy. However, it may be appropriate as a first-line approach when there is more severe depression and when they are under the care of a specialist psychiatrist (NICE, 2005).

To ensure informed consent and shared decision-making, the use of antidepressants should always be underpinned by a discussion with the patient, and family/carer (as appropriate), about the potential level of benefits and harms, including withdrawal, and concordance about initiation and continuation. Greater emphasis is also required on regularly reviewing antidepressant use (supported by adequate resourcing and better use of technology) to monitor how well the treatment is working and any side effects, as well as to ensure that long-term use remains clinically indicated.

Discontinuation of antidepressants should involve the dosage being tapered or slowly decreased to reduce the risk of distressing symptoms, which may occur over several months, and at a reduction rate that is tolerable for the patient. Whilst the withdrawal symptoms which arise on and after stopping antidepressants are often mild and self-limiting, there can be substantial variation in people's experience, with symptoms lasting much longer and being more severe for some patients. Ongoing monitoring is also needed to distinguish the features of antidepressant withdrawal from emerging symptoms which may indicate a relapse of depression.

The following recommendations set out a range of actions to promote optimal use and management of antidepressants.

- The UK Health Departments should implement a system of routine monitoring at patient level to provide comprehensive data on when and why patients (including children and young people) are prescribed antidepressants, that can be used to inform research and the further development of clinical guidelines.

- To support clinicians:
  - national and local educational bodies should ensure there is training available for all doctors on assessing depression and its severity, clinical indications for prescribing, the choice and selection of antidepressants, appropriate dose and duration of treatment, and appropriate withdrawal management
  - there should be greater recognition of the potential in some people for severe and long-lasting withdrawal symptoms on and after stopping antidepressants in NICE guidelines and patient information
  - NICE should develop clear evidence-based and pharmacologically-informed recommendations to help guide gradual withdrawal from antidepressant use
  - UK Health Departments should ensure there is adequate resourcing to reduce the high workload in primary care. This is to ensure GPs have sufficient time and capacity to undertake regular reviews of antidepressant use and appropriate follow-up after discontinuation of antidepressants to monitor withdrawal and detect any signs of relapse.

- Commissioning bodies should:
  - continue to increase the provision of psychological therapies for depression, community support and social prescribing opportunities
  - ensure there is sufficient availability of support services for patients affected by more severe and prolonged antidepressant withdrawal, modelled on existing best practice.

- The UK Health Departments should work with the Medical Research Council, the National Institute for Health Research

and other funding bodies to incentivise high-quality research on:

- which antidepressants are likely to work best for an individual patient (based on their depression subtype, personal characteristics or other markers), the side effects of antidepressants and their magnitude for individual patients, and the dose-response association for different antidepressants
- the comparative benefits and harms of antidepressants relative to non-pharmacological treatment options and how this can vary between patients
- the benefits and harms of long-term antidepressant use
- innovative treatments for depression, including treatments designed to prevent relapse of depression
- the incidence, severity and duration of symptoms on and after stopping antidepressants, and factors contributing to the individual susceptibility to such symptoms, and how best to manage these symptoms.

# Discussion and supporting evidence

## 1. Background

Depression can have devastating consequences, from adverse impacts on mental and physical health, to relationship breakdown and unemployment. It significantly increases the risk and rate of suicide, which itself remains the leading cause of death for males aged 35 to 49 years in England and Wales (Office for National Statistics, 2018). Too many people are not getting the support they need – for example, in England, over a third of adults[1] with depression assessed as requiring intervention do not receive treatment (NHS Digital, 2016) and a quarter of individuals aged 5 to 19 years with emotional disorders (including anxiety and depressive disorders) did not access any service or support in 2017 (NHS Digital, 2018a).

Recommended treatment is based initially on the use of evidence-based psychological treatments (particularly cognitive-behavioural therapy). When an individual does not respond to or engage with this initial treatment, or when they have more severe depressive symptoms[2], antidepressants are a recommended[3] therapeutic option[4] for adults (aged 18 and over) (NICE, 2009). This should always follow discussion with the patient and/or their family/carer about the potential benefits and harms, and relative merits of different treatments, to ensure there is informed consent and shared decision-making. They can be prescribed on their own, or in combination with a high-intensity psychological treatment (i.e. treatments that involve more individual and resource-intensive support). Use among children and adolescents is typically as a second-line treatment option for moderate to severe depression when they are unresponsive to psychological therapy and following assessment by a child and adolescent psychiatrist, but may occasionally be part of initial approaches in more severe depression (NICE, 2005; Hussain *et al*, 2018).

The normal course of antidepressant treatment should last at least six months after full symptom remission. In patients with a history of

1 The 2014 Adult Psychiatric Morbidity Survey of mental health and wellbeing in England found that 61.3% of adults with depression were receiving treatment at the time of the survey.

2 See Appendix 1 for a note on terminology.

3 The guidance predominantly used to inform clinical practice for antidepressant prescribing in the UK is 'Depression in adults: recognition and management' (published in 2009, reviewed in 2013 and currently being updated) and 'Depression in children and young people: identification and management' (published in 2005 and updated in 2017) developed by the National Institute for Health and Care Excellence. While these guidelines are directly applicable to England, they are widely referred to in advice provided in Northern Ireland, Wales and Scotland.

4 While this focuses on depression, antidepressants are also used for other conditions, such as generalised anxiety disorder and panic disorder, obsessive compulsive disorder and post-traumatic stress disorder.

recurrent depression, who are at higher risk of relapse, antidepressant treatment should continue for at least 2 years. There is evidence that some patients are prescribed antidepressants for longer than this (Mars *et al*, 2016).

There are complex factors that affect how antidepressants are used safely and effectively, which have come under increasing scrutiny with the year-on-year rise in prescriptions across the UK (see section 2.2). As with many medications, people benefit to varying extents from their use, and patient experiences can vary substantially. There are also concerns about their long-term use and withdrawal management.

## 2. Challenges with prescribing antidepressants

### 2.1 Efficacy, benefits and harms

The following sub-sections describe the main evidence for the efficacy of antidepressants prescribed for adults, children and adolescents. It is worth noting that a challenge in prescribing antidepressants is that the available research does not inform clinicians about whether an individual patient will benefit from antidepressant use, to what extent, and which type of antidepressant should be tried first. This is not unique to antidepressants or depression, and is seen with other conditions, including many physical health conditions. Clinicians therefore need to use their judgement, training and experience in discussing and agreeing the best approach with patients and/or their family/carers.

It is also important that consideration of the efficacy of antidepressants (i.e. the effectiveness of reducing the symptoms of depression) is weighed against the risk of harm from their use. This can range from common side effects (e.g. agitation, appetite loss, insomnia and sleep problems, erectile dysfunction, dizziness, weight gain) – that generally ease within a few weeks but can persist and be more severe – to uncommon and more serious health risks (such as serotonin syndrome or hyponatraemia in elderly people), as well as withdrawal symptoms (see section 2.3). This further emphasises the need for shared decision-making and informed consent to ensure patients fully understand the relative benefits and risks of antidepressant use in treating depression, as well as the risks and harms of not prescribing.

#### How do antidepressants work?

There is only partial understanding of how antidepressants exert their therapeutic effects, which is not uncommon in medicine – for example, the mechanism of action of paracetamol is not fully understood (Sharma and Mehta, 2014) and the role of metformin in treating type 2 diabetes was only recently identified (Polianskyte-Prause *et al*, 2019).

The primary mode of action for most antidepressants is to target monoamine neurotransmitter function, increasing serotonin or noradrenaline availability, or both, at least initially (Harmer *et al*, 2017). While these changes start to happen relatively quickly, clinical improvement and therapeutic effects can take a few weeks. The original idea that antidepressants 'correct a chemical imbalance in the brain' is an over-simplification, but they do have early physiological effects and effects on some aspects of psychological function.

They can induce changes in the function of brain areas that are associated with the improvement in depressive symptoms. In animal studies they have been shown to increase the number and function of brain cells and the connections between them (ibid). They also exert effects on the processing of emotional information within a few hours of drug administration. Depression is often associated with a 'negative bias' in the way a person looks at the world and processes information: cognitive–behavioural therapy works in part through challenging automatic negative thoughts, and the cognitive bias in depression can also be ameliorated by antidepressant drugs.

It is important to recognise that antidepressants can treat the symptoms of depression but do not directly address any underlying psychosocial causes, which is why their use is often combined with psychological therapies that can improve patients' ability to cope with difficult life situations.

### *2.1.1 Depression among adults*

Many studies show that, on average, antidepressants provide benefits in reducing symptoms (ranging from full recovery to minor or no effects) among adults with moderate to severe depression in the acute phase of illness (Gibbons *et al*, 2012; Undurraga and Baldessarini, 2011; Wilson *et al*, 2001; Fournier *et al*, 2010; Khan *et al*, 2002; Arroll *et al*, 2009; Cipriani *et al*, 2009). They do not typically provide benefit for patients with subthreshold depressive symptoms or mild depression (though they are recommended if subthreshold symptoms have persisted for at least 2 years or if other interventions have not worked). This is based on their efficacy in comparison to placebo (i.e. a substance or treatment with no active component). Broadly, when measured against placebo, antidepressants have been found to be more effective than many medications for physical health problems – for example, the number needed to treat (NNT)[5] for antidepressants and depression is typically 3 or 4, lower than the use of ACE-inhibitors for hypertension and chronic heart failure, thrombolytic drug for acute stroke and metformin for diabetes (Leucht *et al*, 2012).

5 The average number of patients who need to receive the treatment, or other intervention, for one of them to get the positive outcome in the time specified. The closer the NNT is to 1, the more effective the treatment. The higher the NNT, the less effective the treatment.

The most comprehensive recent analysis – conducted by Cipriani *et al* and including 116,477 patients – found that all 21 antidepressants were significantly more efficacious than placebo in reducing depressive symptom severity (by at least 50% from baseline) in adults with major depressive disorder after approximately 8 weeks, with odds ratios between 1.37 and 2.13 (favouring antidepressants) (Cipriani *et al*, 2018).

Some researchers contend that, while antidepressants produce a statistically significant effect on reducing depressive symptoms in the short term, the benefit is comparatively small and potentially outweighed by an increased risk of adverse effects (Turner el al, 2008; Kirsh *et al*, 2008; Moncrieff *et al*, 2004; Jakobsen *et al*, 2017). Others have argued that effects identified in meta-analyses are not clinically significant, and that side effects may confound results (Moncrieff, 2018). However, analysis of subjective mood has shown clear benefit for some antidepressants over placebo, in the absence of side effects (Hieronymous *et al*, 2017). Furthermore, the effect of antidepressants and psychotherapy are similar, when comparing the severity of symptoms before and after treatment (Khan *et al*, 2012).

While there are fewer studies of the efficacy of long-term antidepressant use, there is strong evidence that antidepressants – particularly selective serotonin reuptake inhibitors (SSRIs) – can help relieve the symptoms of chronic depression for many individuals (von Wolff *et al*, 2013), as well as lead to significantly lower rates of relapse (response rate 1.90, NNT=4.4) or recurrence (response rate 2.03, NNT=3.8) of depressive episodes (Sim *et al*, 2015).

This research matches psychiatrists' clinical experience that some patients experience greater benefit, whereas others may receive little or no benefit. Patients report having positive, mixed and negative experiences of using antidepressants, ranging from:

- an overall improvement in levels of depression and quality of life
- to feeling the benefit of functioning better while suffering adverse side effects
- to finding them ineffective with intolerable and harmful side effects (Anderson and Roy, 2013; Buus *et al*, 2012); Dickinson *et al*, 2010; Malpass *et al*, 2009; Schofield *et al*, 2011; Gibson *et al*, 2016; Read and Williams, 2018; Cartwright *et al*, 2016).

In interpreting these findings, it needs to be recognised that antidepressants are not a single class of drug – there are major differences in pharmacological properties between them and how individual patients respond to them. Similarly, depression can be caused by a number of different factors that may in part explain the differential response. These findings also emphasise how antidepressant

prescribing needs to be considered alongside other options, such as psychological therapies, and that they should not necessarily be the first line of treatment, especially in patients experiencing their first episode of depression or with relatively mild symptoms. This is in line with National Institute for Health and Care Excellence (NICE) guidelines (NICE, 2009 – currently being updated), British Association for Psychopharmacology guidelines (Cleare *et al*, 2015) and the Scottish Standards for integrated care pathways for mental health.

Where they are prescribed, it should be based on a discussion with the individual patient about the potential level of benefit and likelihood of adverse and harmful side effects. Similarly, discussions about the best treatment option also need to consider that psychological therapies may not be effective for everyone, and that individuals may not want to engage with psychological therapies and can also report adverse effects with this form of treatment (Nutt and Sharpe, 2007; Crawford *et al*, 2016).

### Research priorities

The limitations of the existing evidence underline the need for further high-quality studies in this area. These studies should focus on:

- which antidepressants are likely to work best for an individual patient and thus should be tried first (based on their depression subtype, personal characteristics or other markers)
- the harmful side effects of particular antidepressants and their impact on individual patients; the potential dose–response association for different antidepressants
- the comparative benefits and harms of antidepressants relative to non-pharmacological treatment options and how this can vary between patients
- the benefits and harms of long-term antidepressant use.

High-quality research is also needed to better inform the protocols for stopping antidepressants (see section 2.3.1).

### *2.1.2 Depression among children and adolescents*

Compared to the research in adults, the efficacy of antidepressants for moderate to severe depression in children and adolescents is less clear. While several studies have demonstrated a potential small benefit compared to placebo (Hetrick *et al*, 2012; Qin *et al*, 2014; Locher *et al*, 2017), the most comprehensive network meta-analysis found little advantage in their use in this age group and noted that only fluoxetine is suitable as the preferred pharmacological treatment for moderate to severe depression, with sertraline and escitalopram

as potentially suitable alternatives if there is no response to fluoxetine (Cipriani *et al*, 2016). It is worth noting, however, that meta-analyses that include large numbers of industry-sponsored studies can affect the picture of antidepressant-efficacy for depression in children and young people (because of methodological limitations and the high number of them compared to non-industry funded studies) (Walkup, 2017). When compared to other treatment options, antidepressants compare favourably – for example, the Treatment for Adolescents with Depression Study (TADS), which remains the only large direct comparison of fluoxetine to cognitive–behavioural therapy, found that the rate of response to fluoxetine (60.6%) was notably higher than that of the psychological therapy (43.2%) at 12 weeks (March *et al*, 2004).

While concerns have been raised about antidepressant use and suicidality (Bridge *et al*, 2007; Food and Drug Administration, 2004; Whittington *et al*, 2004; Weller *et al*, 2005; Fergusson *et al*, 2005; Sharma *et al*, 2016), there is no evidence of increased rates of completed suicide and the highest risk for suicide attempts in depressed adolescents has been found to be prior to the initiation of antidepressant use (Simon and Savarino, 2007). A review of 574 youth suicides reported that 1.6% had been exposed to antidepressants (Dudley *et al*, 2010), and the Utah youth suicide study reported that it was the lack of help-seeking that was implicated in completed suicides, and not the adverse effects of antidepressant treatment (Moskos *et al*, 2007). A study of suicides in England and Wales found that of 285 young people aged under 20 who died by suicide, 16% (47) were receiving antidepressants at the time (National Confidential Inquiry into Suicide and Homicide by People with Mental Illness, 2017). Overall, the risk–benefit ratio of using antidepressants for this age group is relatively favourable. For example, a 2007 meta-analysis found their use to be associated with a significantly increased treatment response rate compared with placebo (61% versus 50%), though the non-statistically significant increased risk of suicidal ideation/suicide attempt compared with placebo (3% versus 2%) indicates the need for careful monitoring of treatment (Bridge *et al*, 2007).

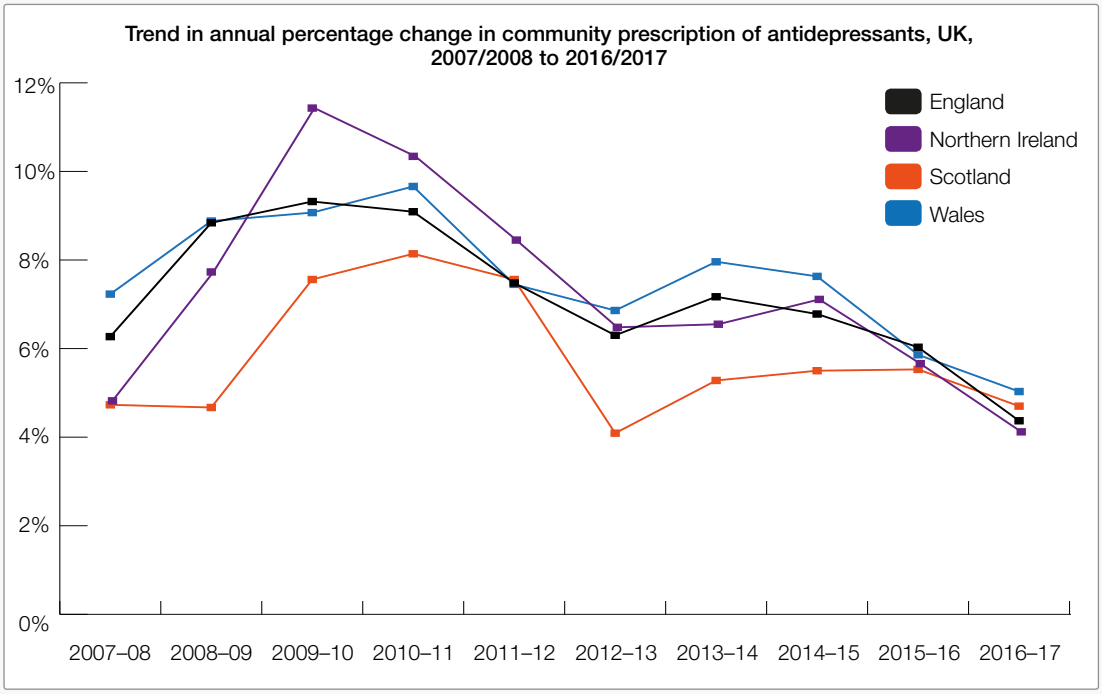
### 2.2 Prescribing as clinically indicated

Antidepressants are mainly prescribed by general practitioners (GPs), and the majority of adults receiving antidepressants (60–85%) use them for depression (Johnson *et al*, 2012; Johnson *et al* 2014; Petty *et al*, 2006). Figure 1 highlights the significantly increasing trend in antidepressant prescribing in the UK, which broadly shows a doubling in the number of prescriptions in 10 years between 2007 and 2017. In England, data for 2018 shows there were 70.9 million prescriptions for antidepressants, which is a 5.0% increase on the previous year (NHS Digital, 2019). Over a similar period, there has been a reported increase in the prevalence of depression among adults and children and adolescents (see Appendix 2); however, this is of a smaller magnitude (in the region of between 30–50% increase in the last few years).

Figure 1 – Antidepressant prescribing in the UK

| Community prescription statistics | | | | | |
|---|---|---|---|---|---|
| | Number of prescriptions | | | | |
| | 2007 | 2016 | 2017 | % change 2016–17 | % change 2007–17 |
| England (NHS Digital, 2018b) | 33,839,594 | 64,703,568 | 67,530,375 | 4.4 | 99.6 |
| Northern Ireland (HSC Business Services Organisation) | 1,525,497 | 2,949,619 | 3,071,021 | 4.1 | 101.3 |
| Scotland* (NHS National Services Scotland, 2017) | 3,654,388 | 6,114,215 | 6,401,661 | 4.7 | 75.2 |
| Wales (Welsh Government, 2018) | 2,725,876 | 5,376,108 | 5,646,645 | 5.0 | 107.1 |

* Data for 2006/07, 2015/16 and 2016/17 respectively




Other analyses:

- Research by the Health Foundation and Nuffield Trust found that there was a 165% increase in the prescribing of antidepressant drugs in England between 1998 and 2012 (an average of 7.2% a year) (Spence *et al*, 2014). There is some evidence that the rate accelerated between 2008 to 2012, during the period of the financial recession.

- A longitudinal study of antidepressant prescribing in 3- to 17-year-olds in the UK found that antidepressant prescribing (first-ever prescriptions) nearly doubled between 2006 and 2015 (from 1.60 to 3.12 per 1000 person years). In 2015, 21% of patients with first-ever prescriptions

**Figure 1 (continued) – Antidepressant prescribing in the UK**

(n=1,721) could be linked to a depression diagnosis, and the incidence of prescriptions linked to a depression diagnosis increased between 2012 and 2015, with an adjusted incidence rate ratio of 1.46 (Sarginson *et al*, 2017).

- An electronic cohort study of routinely collected primary care data in Wales found antidepressant prescribing increased significantly between 2003 and 2013, mainly in older adolescents. Just over half of new antidepressant prescriptions were associated with depression (diagnosis or symptoms) (John *et al*, 2016).

- Analysis of NHS business services authority data shows that 7.1 million adults (one in six adults) were given at least one antidepressant prescription in 2017 in England; individuals aged over 60 were twice as likely as those in their twenties to be using an antidepressant; and there are marked regional variations (e.g. one in five people in Blackpool and Great Yarmouth respectively use an antidepressant, compared to one in ten in London) (Smyth and Goddard, 2018).

- Analysis of data from NHS England, NHS Scotland and the Health and Social Care Board in Northern Ireland found that the number of prescriptions to children increased by 15% in England, 6% in Northern Ireland and 10% in Scotland between April 2015 and March 2018 (Newlan, 2018).

- According to the Organisation for Economic Cooperation and Development (OECD), antidepressant use (defined daily dose per 1,000 people per day) has doubled in the 29 OECD countries between 2000 and 2015, and the UK reports the fourth highest rate (OECD, 2018).

- The Health Survey for England report that 10% of adults (aged 16 and over) used an antidepressant in the last week in 2015/16 (13% of women and 6% of men), and that use was highest in the 55–64 and 75–84 age groups (NHS Digital, 2017).

### *2.2.1 Understanding the rise in antidepressant prescribing*

The absence of a corresponding increase in the prevalence of depression in line with the increase in prescribing rates, or any substantive changes to treatment recommendations, suggests that prescribing practice has changed. A complex and interacting range of factors might underpin this on an individual level, practice level and across broader society.

- While there is evidence that half of all patients with a first diagnosis of depression stop using antidepressants after approximately 7 months, and around a third after 1 or more years (Coupland *et al*, 2015), several studies have found that an increase in the proportion of patients receiving longer-term treatment has contributed to higher prescribing rates (Mars *et al*, 2016; Kendrick *et al*, 2015; Lockhart and Guthrie, 2011; Moore *et al*, 2009). While longer-term use is appropriate for a proportion of individuals (i.e. those with chronic or recurrent depression), there is no comprehensive data on the prevalence of antidepressant prescribing at

patient level and the extent of continuation for longer than clinically indicated. Patients may wish to remain on long-term treatment because of concerns about relapse or the potential difficulty of discontinuing use, and there is evidence that some patients do not have the continuing need for antidepressant use adequately reviewed (Petty *et al*, 2006; Sinclair *et al*, 2014).

- There is evidence that the use of higher doses has contributed to total prescribing growth (Johnson *et al*, 2012; Lockhart *et al*, 2011; Johnson *et al*, 2017). This is despite the research showing that higher doses lack significantly greater efficacy in depressive illness (though not in some anxiety-related disorders) and are associated with a higher risk of adverse side effects (Adli *et al*, 2005; Cleare *et al*, 2015).

- There is variation in the provision of and access to psychological therapies within and between different countries in the UK. This has been suggested as a potential factor in variations in antidepressant prescribing (Meikle, 2016), based on the hypothesis that where these services are not readily accessible, antidepressants are the only, or perhaps quickest, treatment option. While there is limited research in this area, it is worth noting that no significant relationship has been found between primary care antidepressant prescribing and uptake of the Improving Access to Psychological Therapies (IAPT) programme in England (Spence *et al*, 2014; Sreeharan *et al*, 2013), although it could be that increasing use of IAPT has offset further prescribing rises. It is also important to recognise that not all patients will benefit from psychological services and move on to antidepressant treatment, and that the increased availability of psychological therapies will not reduce prescriptions for any individuals who do not want to engage with these services. Similarly, specific patient groups (e.g. lesbian, gay, bisexual, transgender individuals and people with intellectual disabilities) may not be well served by these services or able to access them as easily.

- Wider factors that may have impacted on the rise in antidepressant prescribing include the increased awareness of depression and anxiety by patients and professionals, reflecting how the historically high levels of unmet need are starting to be recognised. Despite the increase in antidepressant prescribing, in England, over a third of adults with depression assessed as requiring intervention do not receive treatment (NHS Digital, 2016).

- The broadening range of indications for which antidepressants are prescribed among adults (Mercier *et al*, 2013; Aarts *et al*, 2016; Wong *et al*, 2016; Wong *et al*, 2017; Vijay *et al*, 2018) and children (Sarginson *et al*, 2017; John *et al*, 2016) (such as generalised anxiety disorder, panic disorder, obsessive compulsive

disorder and post-traumatic stress disorder, as well as for non-mental health disorders such as pain) are known to have affected the levels of antidepressant prescribing.

- A 2014 QualityWatch study found several factors that influenced variation in prescribing rates between areas in England, including demographic features (antidepressant prescribing is higher in areas where there is a higher proportion of patients who were aged 65 and over, female and white), characteristics of the GP practice (such as their propensity to prescribe), and wider socioeconomic factors (such as unemployment rates) (Spence *et al*, 2014).

### *2.2.2 Supporting optimal prescribing*

The variation in regular monitoring of antidepressant prescribing at a patient level makes it difficult to comprehensively assess the extent to which the rise in prescribing is clinically indicated. This needs to be addressed to better understand when and why patients are prescribed antidepressants for depression or for other conditions.

The available evidence does suggest the need for improved monitoring of patients' long-term antidepressant use. This will require better resourcing to tackle the high workload in primary care and ensure GPs have the time and capacity to undertake appropriate assessments and discussions with patients before starting treatment, as well as regular reviews of patients who are prescribed antidepressants. The increasing focus on technology and digital innovation should be used to support this through relevant alerts, reports and data collection, and there could be an important role for specialist nurses. This will help identify and reduce the number of patients continuing to take them in the absence of clinical need, with appropriate support and advice, which has been estimated to be as high as one-third of patients on long-term antidepressant therapy (Cruickshank *et al*, 2008).

Whether or not the availability of psychological therapies directly impacts on prescribing rates, patients with common mental disorders (such as depression and anxiety) should have comprehensive access to these services. Use of these therapies in combination with antidepressants, or as an initial therapeutic option, is important in supporting patients – for example, the combination of preventive cognitive therapy with antidepressant treatment has been shown to result in a 41% relative risk reduction in relapse or recurrence of major depressive disorder compared to antidepressants alone (Bockting *et al*, 2018). Conversely, it may be that antidepressant use initially helps reduce depression symptoms enough for an individual to engage with psychological therapies, or that, for some individuals, there may be no willingness to engage with these services.

### 2.3 Managing withdrawal

Stopping antidepressants can cause discontinuation/withdrawal symptoms (see Box 1 for a discussion on terminology) (Wilson and Lader 2015; Fava *et al*, 2015; Renior *et al*, 2013; Horowitz and Taylor, 2019). While they can occur with all types (Cleare *et al*, 2015), there are differences between classes of antidepressant (e.g. symptoms are particularly marked on stopping paroxetine or venlafaxine) (Fava *et al*, 2015). These symptoms are a common reason why patients report mixed and negative experiences of taking and stopping antidepressants (Gibson *et al*, 2016; Read *et al*, 2018; Cartwright *et al*, 2016).

Current NICE guidelines note that these adverse effects "…are usually mild and self-limiting over about 1 week, but can be severe, particularly if the drug is stopped abruptly" (NICE, 2009). However, there is a clear patient voice, as well as support groups, charities and organisations that have highlighted that adverse effects can be particularly severe and/or long-lasting (BMA, 2015; APPG for Prescribed Drug Dependence, 2018a; APPG for Prescribed Drug Dependence, 2018b; PE01651; P-05-784).

While there is some published research showing that symptoms on and after stopping antidepressants can persist for several weeks and longer (Horowitz and Taylor, 2019; Fava *et al* 2018), there are limited high-quality data in this area. The best evidence for evaluating discontinuation symptoms after acute treatment comes from specifically-designed randomised placebo-controlled trials, with a staggered double-blind discontinuation, so possible expectancy and other non-specific effects are considered. However, most antidepressant clinical trials were not designed to look carefully at withdrawal and generally had a shorter duration of treatment and follow-up than many patients now receive in clinical practice.

A 2018 review (Davies and Read, 2018) identified six randomised controlled trials (with a total collective number of 1,465 participants) which when combined show a weighted average withdrawal incidence rate of 50.7% (Montgomery *et al*, 2005; Oehrberg *et al*, 1995; Rosenbaum *et al*, 1998; Sir *et al*, 2005; Tint *et al*, 2008; Zajecka *et al*, 1998). When considered alongside a wider range of studies identified in the review (with varying methodologies including participant surveys in which participants were self-selected, and therefore of unknown generalisability, and varied sample sizes), the authors estimated that an average of 56% of patients who stop or reduce antidepressant use experience withdrawal symptoms, with 46% of these reporting severe symptoms, and a significant proportion experiencing symptoms for several weeks, months, or longer (Davies and Read, 2018). The accuracy of these estimates is the subject of much debate (Jauhar and Hayes, 2019; Davies and Read, 2019), and the estimates are considerably higher than those from the Committee on Safety of Medicines (Weller *et al*, 2005).

However, while there are not comprehensive data, the potential for and existence of more severe and long-lasting symptoms reported by patients needs greater recognition, including in NICE clinical guidelines and patient information. The recent evidence should also be taken into account by prescribing clinicians in discussion with patients before embarking on antidepressant therapy. High-quality research is needed to comprehensively understand the incidence, severity and duration of symptoms associated with withdrawal of antidepressant use, and the factors contributing to the individual susceptibility to severe withdrawal effects.

### Box 1 – Discontinuation symptoms, withdrawal and dependence

**There are different views on whether antidepressant use can lead to dependence, which may reflect the different ways these terms are used clinically and in public discourse. While NICE guidelines recognise the existence of discontinuation symptoms in relation to stopping antidepressant use, these are often referred to as 'withdrawal symptoms' (or may represent a 'withdrawal syndrome'). These terms are likely to be referring to the same adverse effects. These effects need to be distinguished from symptoms of relapse or recurrence of the original condition for which they were prescribed to ensure the former is not mistakenly attributed to the latter. This is particularly important where depressive symptoms return concomitantly with a reduction or cessation of antidepressant use. However, it is important to note that some of the symptoms reported by patients on discontinuation of antidepressants are not typically features of depressive disorder and therefore, most likely, represent withdrawal symptoms.**

**There is a public perception that these symptoms are indicative of drug dependence. A clinical diagnosis of dependence (or having a dependence syndrome) requires various criteria to be met in addition to withdrawal symptoms (including a compulsive desire to take the drug and difficulty controlling use despite evidence of harm, and the development of tolerance such that more of the drug is needed to produce the same effect). These are characteristic of drugs with dependence potential, such as alcohol, opioids and cocaine, and from a clinical perspective, antidepressant use is not associated with dependence in these terms. However, for some patients, the experience of withdrawal symptoms is perceived as equivalent to being dependent, and potentially is a motivation to continue antidepressant use (Leydon *et al,* 2007).**

**The Committee on Safety of Medicines' systematic review of the clinical, pre-clinical and experimental research on dependence and addiction liability for SSRI antidepressants (Weller *et al*, 2005) concluded that they are not dependence-**

**Box 1 (continued) – Discontinuation symptoms, withdrawal and dependence**

**producing in the same way that alcohol, stimulants, opioids and benzodiazepines are. This does not, however, negate the reported patient experiences of more severe antidepressant withdrawal, but should provide reassurance that antidepressants do not share the addictive properties of known dependence-producing drugs. It is also worth noting that many other medicines, including those used to treat physical health conditions, have recognised withdrawal syndromes without producing dependence (e.g. steroid withdrawal syndrome) (Margolin *et al*, 2007; Bhattacharyya *et al*, 2005).**

### *2.3.1 Improving withdrawal management*

The possibility of withdrawal symptoms occurring emphasises the importance – as highlighted in NICE guidelines (NICE, 2009) – of clinicians taking the following steps:

- explaining to patients the potential of adverse effects, including withdrawal, as well as the potential benefits, before commencing antidepressant treatment
- ensuring they advise patients to not omit doses or stop use abruptly or rapidly
- discussing what symptoms to expect
- when withdrawing an antidepressant, doing this gradually
- monitoring for these symptoms and considering reintroducing the original antidepressant (or another antidepressant with a longer half-life from the same class) if symptoms are severe.

In managing withdrawal, gradual tapering of the dose should be recommended. There is broad consensus that the longer antidepressants have been used, the longer period of time treatment should be tapered. When a drug has only been used for a short period, has a long half-life (fluoxetine), or if there are serious side effects with the drug, more rapid withdrawal may be appropriate. However, a significant challenge for clinicians is the lack of a defined optimal rate of tapering to prevent discontinuation symptoms, and a lack of guidance and advice in this area (Wilson *et al*, 2015).

Current NICE guidance advises that this should be '…normally over a 4-week period, although some people may require longer periods…' (NICE, 2009). As this advice is ambiguous, it is notable that

the updated version of these guidelines proposed that the dose be slowly reduced '…at a rate proportionate to the duration of treatment. For example, this could be over some months if the person has been taking antidepressant medication for several years' (NICE, 2018). However, this is an area where patients and clinicians require ongoing support and would benefit from clear, evidence-based tapering recommendations.

### Research priorities

More high-quality research that can guide clinicians on which antidepressants are more or less likely to be associated with withdrawal/discontinuation symptoms among individual patients, as well as distinguish these effects from relapse/recurrence, is also needed.

### *2.3.2 Support for stopping antidepressants*

It should be part of standard medical practice at the end of treatment to taper the dosage of an antidepressant before stopping, unless there are clinical indications for more rapid withdrawal (as noted previously). General practitioners and psychiatrists should be able to monitor and provide support for the symptoms which might occur on and after stopping antidepressant treatment. This requires time and resource to create a supportive environment where patients can consider withdrawal in an informed manner. As depression can often co-exist with other physical and mental health conditions – and interact with wider social factors that affect an individual's circumstances – more guidance is needed on how to support withdrawal in these complex situations. In patients who have more severe or prolonged withdrawal symptoms, a more gradual reduction of dose is recommended. In addition, there should be more support services for those affected by more severe and prolonged antidepressant withdrawal.

# Appendix 1 – Terminology

Depression is a heterogeneous condition broadly referring to the absence of a positive affect and experiencing a range of associated emotional, cognitive, physical and behavioural symptoms. It is more than transient sadness, but a feeling of being sad, low and unhappy for weeks, months and longer. The severity and type of symptoms can vary widely between individuals and can change over time. Depression can be classified as mild, moderate or severe, although the thresholds for these forms differ between the International Statistical Classification of Diseases (ICD) and The Diagnostic and Statistical Manual of Mental Disorders (DSM).

According to NICE guidelines:

- Mild depression is when a person has a small number of symptoms that have a limited effect on their daily life.
- Moderate depression is when a person has more symptoms that can make their daily life much more difficult than usual.
- Severe depression is when a person has many symptoms that can make their daily life extremely difficult (NICE, 2009).

The terminology also differs between these classification systems, with the DSM using the term 'major depressive disorder' and the ICD referring to 'depressive episodes'. Patients may also have 'sub-threshold depressive symptoms' that do not meet these criteria. It is worth noting that many of the studies on the use and efficacy of antidepressants use the DSM criteria.

# Appendix 2 – Data on depression prevalence in the UK

The following data provide an indication of trends in depression prevalence in the UK. As it is obtained from different reporting systems and types of data, it does not provide a complete picture. For example, Northern Ireland, Wales and Scotland do not have a bespoke psychiatric morbidity survey as in England, and data from their respective health surveys is typically on the overall prevalence of a mental health condition. There are also differences in the reporting periods for Quality and Outcomes Framework (OQF) data.

### England

- According to the 2014 Adult Psychiatric Morbidity Prevalence Survey, depression among adults aged 16 to 64 in England increased from 2.6% in 2007 to 3.8% in 2014 (McManus *et al*, 2016). QOF prevalence rates for depression among adults aged 18 and over in England increased from 11.2% in 2010/11 to 11.7% in 2011/12, and, following a change in recording methodology, increased from 5.8% in 2012/13 to 9.1% in 2016/176.

- According to the 2017 Mental Health of Children and Young People survey, 1.2% of children aged 5 to 15 years in England (1.7% of girls and 0.8% of boys) had depressive disorder, compared to 0.8 in 2004 and 0.9 in 1999 (NHS Digital, 2018a).

### Northern Ireland

- QOF data show that the prevalence rates for depression among adults aged 18 and over in Northern Ireland increased from 8.6% in 2006/07 to 12.4% in 2011/12, and, following a change in recording methodology, increased from 6.5% in 2012/13 to 10.3% in 2017/18 (Department of Health, 2017).

### Scotland

- The 2015 Scottish Health Survey reported that in 2014/2015, one in ten (10%) adults exhibited two or more symptoms of depression, indicating moderate to high severity. This level is similar to that reported in the previous survey periods of 2008/2009 (8%), 2011/2012 (8%) and 2012/2013 (9%) (Brown *et al*, 2016).

- QOF data show that the prevalence rates for depression among

6 Data obtained from NHS Digital statistics Quality and Outcomes Framework, Achievement, prevalence and exceptions data (available at: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data) and Quality and Outcomes Framework, Achievement data (available at: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-data).

adults aged 18 and over in Scotland increased from 6.2% in 2006/07 to 9.0% in 2011/12, and, following a change in recording methodology, increased from 5.2% in 2012/13 to 6.8% in 2015/16 (Information Services Division, 2016).

### Wales

- QOF data show that the prevalence rates for depression among adults aged 18 and over in Wales increased from 7.3% in 2006/07 to 9.5% in 2011/12, and, following a change in recording methodology, increased from 5.0% in 2012/13 to 7.7% in 2015/16 (Statistics for Wales, 2017).

### Other

- The 'Measuring national well-being: Life in the UK: 2016' survey reported that 19.7% of people in the UK aged 16 and older showed symptoms of anxiety or depression in 2014 – a 1.5% increase from 18.3% in 2013 (Evans *et al*, 2016).

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