How long should an episode of depression be treated for and at what dose of antidepressants?

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Abstract

Current depression guidelines are reviewed; these recommend the continuation of antidepressants at the dose that achieved response for at least a further six months, depending on patient circumstances and previous history. The dose can then be reduced gradually: the more slowly the reduction, the less likely withdrawal effects will be. If severe withdrawal symptoms occur, changing to fluoxetine, which has a long half-life, and decreasing this slowly is best. If the patient is at heightened risk of relapse, or if relapse would have serious consequences, the antidepressant should be continued. The duration of treatment depends both on the life situation and on the level of relapse risk, both of which need careful management. Learning opportunities for the management of depression need to be multi-professional and case-based. Consultation-liaison can be one way to achieve this when, for example, a local mental health professional can give case-based advice to the primary care team. However, the evidence base for changing GP behaviour is weak, even when GPs are involved in adapting and extending depression guidelines for local use.

Introduction

GPs and practice staff have continuing contact with people with major depressive disorder (MDD); 25% of people will develop this condition at some point in their lives. In addition, there are many other patients every day who are dispirited, suffering "anomie", "ennui", low mood, disinterest, low confidence and poor energy, often associated with fearfulness, tension and anxiety. For the latter group, with circumstantial distress, GPs and practice staff can provide understanding, and perhaps reframe reactions to life situations (e.g. about aging, losses of physical health, employment, finances, relationships etc.): "The most common but perhaps least recognised way in which primary care practitioners alleviate the mental health problems presented by their patients is by acknowledging the reality of their experience and offering them hope of an alternative" (1). For the former group with major depressive illness, GPs and practice staff must provide regular contact. Human beings communicate best when they are comfortable with one another, and optimal contacts will be with the same staff member. A common denominator of all successful psychotherapies is the quality of the client–therapist relationship. In primary care, this therapeutic rapport allows reactions to circumstances to be ameliorated through supported problem-solving and behavioural activation, including positive lifestyle changes such as improved diet and exercise. However, it may also be necessary to enlist other professionals to provide more specialist therapies (e.g. cognitive behavioural therapy, interpersonal therapy), social and peer support and financial advice.

Antidepressants are an important option for treatment. The National Institute for Health and Care Excellence (NICE) recommends antidepressants for persistent low-grade symptoms which do not respond to psychosocial interventions (2). For moderate and severe depression, NICE recommends a combination of antidepressant treatment and psychotherapy (2). Perhaps in these situations biology and stress have resulted in a neurophysiological change which antidepressants correct. Questionnaires can be used to gain an estimate of severity, but the degree of impairment in day-to-day life is the best indication. Following the exploration of different psychological and pharmacological approaches, and when the optimal type and combination has been found, the long-term support that the person will need must be considered.

In this paper, we focus on the use of antidepressant medication in those patients who are known to have benefitted from it in the treatment of their acute major depressive episode. We discuss how long to

continue antidepressants to prevent relapse of the index episode and to reduce the likelihood of future episodes. The issue of how to stop antidepressants to minimise withdrawal phenomena is also addressed.

Relapse prevention

There is a high risk of relapse after a depressive episode, particularly in the first six months. The risk of relapse decreases with the amount of time in remission. Of people who have had an episode of depression, 50-85% will have a second episode, and 80-90% of those who have had a second episode will go on to have a third episode (3). All patients need to be assessed for their potential risk of relapse. Important risk factors include the presence of residual symptoms of depression, the number and severity of previous episodes, and both the duration and degree of treatment resistance of the most recent episode (4). Ongoing life events and difficulties, particularly around relationships, will play a role. Over 50% of those with recurrent unipolar depressive episodes have a personality dysfunction (5), which can be assessed using a brief questionnaire (6). Other factors known to increase the likelihood of a depressive recurrence include: a family history of depression, recurrent dysthymia, female gender, and the lack of a confiding relationship (3).

When patient and physician decide that medication is indicated, the first task is to find the best antidepressant. This implies choosing a drug which is effective in achieving remission of symptoms and ideally has no adverse effects. For patients who only have a partial response to a medication it is important to be sure that an alternative will not achieve more. It is not satisfactory for a patient to be prescribed, for example, citalopram with only slight benefit and to be left on that drug. In secondary care, psychiatrists frequently find that depressed patients improve with judicious medication change. It is important assertively to explore reasonable options as listed in the relevant NICE guidelines; for example SSRIs, mirtazapine, or lofepramine (2). NICE recommends two-to-four-weekly follow-up in these early stages for this process to occur. If the depression has marked biological symptoms, such as early-morning waking prior to treatment or diurnal mood variation, or is not obviously psychodynamic in origin then an active search for the effective drug is indicated (2). Many cases of moderate depression are probably pharmacologically under-treated, and dysthymia (more than two years of sub-syndromal depression) has a high response to antidepressants (NNT 4.5) (7).

It is important not to ignore persisting cognitive symptoms (e.g., poor concentration, information processing or memory), which can be symptoms of a partially-treated depressive process. Before assisting patients to manage continuing symptoms, it is important to be certain that they do have to endure them. Psychiatrists can provide advice on the choice of antidepressant and how to swap from one to the other. With regard to adverse effects, a drug can often be found which does not cause any. For example, the "numbness" patients describe on some antidepressants will not occur with others, and sexual adverse effects can resolve with a change of drug.

Once the best response, ideally remission, has been achieved, it is generally recommended that antidepressants should be continued at the same dose that achieved the response for at least a further 4-6 months (2-4, 8-11). The British Association of Psychopharmacology (3) has refined this recommendation. They recommend that medication-responsive patients should be kept on antidepressant medication at the acute treatment dose for a duration that is determined by the risk of relapse. In patients at lower risk of relapse (e.g. first-episode patients without other risk factors), the duration should be at least 6-9 months after full remission. The duration of treatment in other cases should be tailored to the individual relapse risk; consider a duration of at least one year after full remission in patients with any increased risk of relapse; for example, those with ongoing life difficulties. In higher-risk patients (e.g. more than five lifetime episodes and/or two episodes in the last few years), at least two years treatment should be advised and for most, long-term treatment should be considered. There is evidence that in older people continued antidepressant treatment halves relapse rates.

The life situation of the patient should be taken into account. For example, a woman with young children who considers her ability to care for her children is markedly compromised when she is depressed, and feels tested by motherhood, may prefer to continue medication. A student approaching testing exams may want to take all steps to prevent a relapse if a previous depressive episode derailed their academic program. In both cases continuing medication, with monitoring, would be reasonable.

When relapse was the subject of an international systematic review published in the Lancet (12), it was found that antidepressants significantly reduced the subsequent risk of a relapse of depressive disorder. Continuing treatment with antidepressants reduced the odds of relapse by 70%. The average rate of relapse on placebo was 41% compared with 18% on antidepressant medication.

People with single-episode depression who are left with residual symptoms and have concurrent physical illness or continuing psychosocial difficulties (13) may need antidepressant medication for a year or more rather than 4-6 months. The question that must be asked is whether any residual symptoms are treatable with a change of medication or a focus on psychotherapy. NICE recommends regular reviews of the treatment plan if improvement is not occurring or has not been maintained (2).

Cognitive behavioural therapy added to medication should be standard for those with moderate or severe episodes, those with residual symptoms and those at higher risk of relapse. Mindfulness-based cognitive therapy (MBCT) added to usual treatment may help to prevent relapse in those who have had more than three previous depressive episodes (3). In the 50% of patients with recurrent depressive episodes who have a personality dysfunction, perhaps indicated by difficulties with relationships or low self-esteem, more in-depth psychotherapies, such as schema work or cognitive analytical therapy, may be valuable (4).

Stopping antidepressants

Most patients can stop their medication without difficulty, following steady dose reductions over a month or more. Generally, withdrawal symptoms are mild and short lived. Fewer than 5% have severe and sometimes persistent withdrawal symptoms. Those patients taking paroxetine or venlafaxine are most prone to this because of the short half-lives of these drugs, but any patient taking antidepressant therapy is at risk of withdrawal symptoms. When stopping antidepressants, it is important to alert the patient to the withdrawal symptoms and to distinguish these from relapse, which tends to occur later. If withdrawal symptoms are prolonged and disabling then changing to fluoxetine and reducing by 2 mg per week, using the liquid preparation, can be an effective management.

The effect of guidelines on GP prescribing

Learning opportunities for the management of depression, such as Trailblazers (14), the earlier RCGP program for training GP leaders in mental health, need to be multi-professional and case-based. Consultation-liaison can be one way to achieve this when, for example, a local mental health professional can give case-based advice to the primary care team. Although, in principle, teaching GPs about the guidelines for depression management should be valuable, studies have not shown that this is necessarily the case (15,16), suggesting that further consideration and planning is necessary in this area.

Conclusion

Current guidelines recommend the continuation of antidepressants at the dose that achieved response for a further six months. The dose can then be gradually reduced; the more slowly that this occurs, the less likely it is that withdrawal symptoms will be experienced by the patient. If severe withdrawal symptoms occur, changing to fluoxetine, which has a long half-life, and decreasing the rate of withdrawal can result in successful discontinuation. If the patient is at heightened risk of relapse, or if relapse would have serious consequences, for example in the context of approaching important exams or childcare, then the antidepressant should be continued. The duration of treatment continuation depends both on the life situations that have to be managed and on the level of relapse risk.

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