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DO GENERAL PRACTITIONERS FOLLOW GUIDELINES ON THE USE OF ANTIDEPRESSANTS TO TREAT DEPRESSION? CAN THE SITUATION BE IMPROVED?

Shentong Wang[1], Katherine Alice Wilkinson[1] & Mark Agius[1,2]

[1]Clare College Cambridge, Cambridge, UK

[2]Department of Psychiatry, University of Cambridge, Cambridge, UK

SUMMARY

Several papers have been written to show that General Practitioners do not always prescribe according to the guidelines despite the availability of guidelines regarding the dosage and length of treatment with antidepressants to treat a depressive episode. Here we review the evidence as to whether GPs follow antidepressant guidelines, covering the data between 1996 and the present day, and discuss the implications of this evidence. We then propose solutions which could be used to improve adherence to the guidelines.

We propose as one solution the development of joint Doctor-Practice Nurse clinics for the treatment of depression. The outcomes of these clinics should be auditable against the guidelines. Such a solution, when linked with easy access to advice and referral to Secondary Care Psychiatry specialists, argues for a collaborative care or shared care program for the treatment of depression in Primary Care.

Key words: *depression - anti-depressants - primary care - collaborative care*

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INTRODUCTION

Despite the availability of guidelines regarding the dosage and length of treatment with antidepressants for a depressive episode, it has been repeatedly shown that General Practitioners do not always prescribe according to the guidelines.

In this article, we review the evidence as to whether GPs follow antidepressant guidelines, covering the published data between 1996 and the present day, and discuss the implications of this evidence. We then propose solutions which could be used to improve adherence to the guidelines.

THE EVIDENCE

The recognition and management of depression in General Practice has been influenced by the advice given in Paykel and Priest's 1992 paper (Paykel 1992), which was then taken into the NICE guidelines. The NICE guidelines, reviewed in 2013, current advise medication for the treatment of depression to be prescribed for at least six months, including two months of treatment after diagnosis followed by four months after remission of an episode of depression, to prevent relapse. Furthermore the guidelines advise that treatment be continued for two years if the patient is under significant risk of relapse. A number of studies over several years have suggested that these guidelines frequently have not been strictly followed by General Practitioners, and this may be limiting the effectiveness for the treatment of depression. These papers have discussed the causes and potential solutions to this issue.

The initial evidence that many GPs prescribed antidepressants at too low a dose for too short a time was Donoghue and Tylee's article on the use of antidepressants in the treatment of depression (Donoghue 1996). In the time period which they analysed, eighty-eight percent of prescriptions of older tricyclics (TCAs) by GPs were at doses below those recommended by consensus guidelines. However, SSRIs and newer antidepressants appeared to be prescribed at effective doses. It was also demonstrated that both regarding TCAs and SSRIs, the medication was not prescribed for the recommended six months but for a much shorter period of time. The study combined data from three different sources: PACT (prescribing analysis and cost) data, GP notes and DIN-LINK database from Compufile. Between the three sources, nearly two million patient records were analysed (Donoghue 1996). As suggested by the authors, the cross-sectional nature of the study meant that the doses calculated did not take into consideration their position on the treatment timeline, i.e. whether they were starting doses. It was therefore considered unlikely that titration could account for the proportion of low doses. SSRIs and newer antidepressants were recommended in the conclusion to be first line treatment for depression as a short term solution, since these are already administered at effective doses. It is worth noting that it is not too surprising that SSRI antidepressants were prescribed at adequate doses, since the tablet size of all SSRIs is exactly the recommended dose for these drugs, while TCAs are produced in tablet sizes some of which are lower than the therapeutic dose. Concerns raised by the study caused training programmes to be developed in order to improve the capability of GPs to treat depression with antidepressants (Tylee 1999).

The appropriate dose of antidepressants which should be recommended by guidelines needs to be established by appropriate studies. This is particularly so for older tricyclic antidepressants, in 'working age' patients, where in the past there has been some advocacy of the use of lower dosage.

A Meta-analysis of thirty-three studies of antidepressant treatment was carried out in 1999 (Bollini 1999).

The aim of this study was to determine whether high doses of antidepressants are more effective than low doses, and how safety is affected by dose. They identified trials comparing two or more doses of the same antidepressant and all antidepressants administered were converted to the equivalent dose of imipramine. They found that the dose level of 100-200 mg imipramine equivalents showed an average improvement of 53% by 'intention-to-treat' analysis. Higher doses were not accompanied by increased efficacy, while lower doses showed reduction in efficacy. Adverse events significantly increased with dose. It was concluded that with a low dose of antidepressants, clinicians trade off a slightly reduced chance of improvement for a higher chance of avoiding adverse reactions. Thus this meta-analysis emphasized the need to use effective doses of antidepressants, including tricyclics.

The dosage of antidepressants to be used may sometimes vary with such circumstances as the age of the patients, as older patients may need to be prescribed lower doses. Research into the effects of antidepressants in older patients (Old Age Interest Group 1993) has provided some evidence for the efficacy of lower than recommended doses (75mg) in the elderly but the sample size analysed was small (only fifty-eight patients by the end). In this study of 69 patients who had recovered from major depressive disorder and entered a two-year double-blind placebo-controlled trial of dothiepin, survival analysis revealed that dothiepin reduced the relative risk of relapse by two and a half times. This establishes a recommendation that elderly persons who recover from a major depressive illness should continue with antidepressant medication for at least two years. The conclusions of a Cochrane review in 2012, (Wilkinson 2012) repeated in 2016 (Wilkinson 2016) are uncertain, in that the conclusion was that 'The long-term benefits of continuing antidepressant medication in the prevention of recurrence of depression in older people are not clear and no firm treatment recommendations can be made on the basis of this review (Wilkinson 2012).' Furthermore it was said that continuing antidepressant medication for 12 months appeared to be helpful but only on the basis of three small studies using relatively few participants and differing classes of antidepressants in clinically heterogeneous populations (Wilkinson 2012). The updated meta-analysis of 2016 reported again that 'This updated Cochrane review supports the findings of the original 2012 review (Wilkinson 2016). The long-term benefits and harm of continuing antidepressant medication in the prevention of recurrence of depression in older people are not clear and no firm treatment recommendations can be made on the basis of this review' (Wilkinson 2016).

However, this discussion regarding treatment of depression in the elderly does raise one important issue. This is that a study simply assessing prescription data abstracted from written prescriptions, as the Donoghue 1996 study was, can only give a rough indication of the prescribing habits of doctors; in such a study we have no clarity as to whether the prescriptions are for 'working age' patients (usually age 16 to 65), how many were for elderly patients requiring maintenance, and indeed other indications, such as amitriptyline for improving sleep (in which case the dose will be much lower than the dose for depression).

Over time, many sets of guidelines for the diagnosis and treatment of common mental health problems have been published e.g. the Bedfordshire Guidelines for Primary Care Mental Health (Agius 2003) and the WHO guide to Mental Health in Primary Care (Goldberg 2000). These guidelines are helpful and generally well received, but the delivery of sets of guidelines to GPs without any formal education package did not improve diagnosis or management of depression as shown by Thompson et al (2000). Croudace has demonstrated this same weakness of guidelines with a study of the impact of the WHO ICD-10 guide (Croudace 2003). A series of standards have been proposed by Agius et al (2005) addressing responses to common mental health problems and providing clarification for what is considered to be adequate primary care in mental health.

However, the fact remains that a recent study has shown that in a database of 237 Scottish practices, there is still huge variation in the time for which patients receive antidepressants when they are treated for depression (Burton 2012). Again prescription data is used to assess compliance with guidelines. A total of 28 027 (2.2%) patients commenced antidepressant treatment during the year studied; 75% continued beyond 30 days, 56% beyond 90 days, and 40% beyond 180 days (Burton 2012). Treatment was less likely to be continued in patients from areas of high socioeconomic deprivation and in those for whom the GP recorded no relevant diagnostic code. Duration of treatment was also shorter in younger patients (Burton 2012).

The effect of following guidelines for treatment of depression was examined in a more recent study (Burton 2015) and it was concluded that the factor that had the most impact on reducing early antidepressant treatment discontinuation and encouraging a more successful outcome was diagnostic coding. A large NHS database was used and thus analysis performed was fairly reliable but as suggested by the authors, it is possible that coding and prolonged treatment are both indicators of severity. However, the differences in severity of depression in patients at the practices were not considered to be significant in terms of influence of coding rates.

Burton et al. concluded that 'Encouraging coding and structured follow-up at the onset of treatment of depression is likely to reduce early discontinuation of antidepressant treatment and improve outcomes' (Burton 2015).

Similarly, in a study by Upton et al. (1999), it was observed that although guidelines had no impact on the overall detection of mental disorders or prescription of antidepressants, there was a significant increase in the number of patients diagnosed with depression. GPs also made a greater use of psychological interventions and so it was concluded that despite there being no certainty in the success of guidelines bringing out change, there were some areas that were more susceptible than others (Upton 1999).

The mixed messages of the effectiveness of guidelines throws a certain amount of doubt on the absolute necessity of their usage but from the studies mentioned, it seems that following guidelines is more likely to secure positive patient outcomes. However it is clear that the distribution of guidelines per se cannot be seen as a substitute for the continued developmental training for primary care doctors and staff - a statement reiterated in Agius' proposed standards.

There have been some studies that compare the different treatment received by patients from primary care centres and from psychiatrists. Simon et al (2001) reported a US study comparing patients treated for depression in primary care with patients treated by specialists. At baseline, patients seen by psychiatrists had slightly higher levels of functional impairment and a tendency to have used specialist care before the study (Simon 2001). In follow-up, psychiatrists' patients made more frequent follow-up visits, so that the proportion making 3 or more visits in 90 days was 57% vs 26% for primary care physicians' patients (Simon 2001). However, the proportion of patients receiving antidepressant medication at an adequate dose for 90 days or more was similar in both groups (49% vs 48%) (Simon 2001). The 2 groups showed similar rates of improvement in all measures of symptom severity and functioning (Simon 2001). The study concluded that although psychiatrists' patients made more frequent follow-up visits, the proportion of patients receiving antidepressant medication at an adequate dose were very similar (Simon 2001), with about 50% of patients not receiving antidepressant medication at an adequate dose. This similarity suggests that there is widespread deviation from guidelines throughout healthcare providers both in primary and in secondary care (Simon 2001). The reasons behind GPs' reluctances to follow guidelines are widespread and can be derived from a number of articles over the years. A major reason behind the prescription of lower doses for tricyclics is the fear of cardiac side effects.

Another major reason for the prescription of lower than optimal doses for tricyclics is most likely to be because of risks of toxicity, which one such study (Cheeta 2004) investigated in the main classes of antidepressants. Their results showed that most deaths were due to suicide, with SSRIs being associated with a significantly lower risk than other types of antidepressants. Tricyclic antidepressants (TCAs) accounted for more drug mentions than did other antidepressant drugs (Cheeta 2004).

Ninety three % deaths from SSRIs occurred in combination with other drugs, especially TCAs (24.5%) (Cheeta 2004). Patients who were linked with combinations of antidepressants were significantly more likely to have had a history of drug misuse (Cheeta 2004). It was suggested that when combination therapy is used, patients should be screened for a history in drug use/misuse (Cheeta 2004). However, if combinations of anti-depressant classes are required e.g. in the case of 'resistant depression', patients should be referred to secondary care (NICE 2016). There are further NICE guidelines providing advice about doses for treatment when used in combinations (NICE 2016).

Furthermore Burton et al's study (Burton 2015) suggested that a reason for the small percentage of coding for depression stems from aspects of performance related pay in the QOF. There is also a large degree of overlap between depression and anxiety disorders, which further complicates diagnosis and therefore, raises issues as to which treatment guidelines to follow. Indeed, in many patients, Anxiety disorders are known to be co-morbid with Depression, whether unipolar or bipolar, to the extent that Anxiety with Depression is a diagnosis with a specific code in ICD 10. There must be a question about whether GPs have the necessary skills, both regarding diagnosis and treatment, to treat patients with several co-morbid disorders.

A different study into the prevalence of self harm (Donovan 2000) compared the frequency of deliberate self harm (DSH) in patients prescribed TCAs and SSRIs prior to the DSH event. Results showed that significantly more events followed SSRI prescription compared to TCAs (Donovan 2000) and so it was concluded that merely prescribing overdose-safe antidepressants were unlikely to reduce overall morbidity (Donovan 2000). Overcaution in only one aspect of the possible factors resulting in morbidity may therefore be counterproductive.

DISCUSSION

The fact that there continues to be important disparities between dosages of antidepressants prescribed, and time for which they are prescribed, as well as outcomes of treatment for depression between practices is a matter for concern.

Such disparities were reported by Tylee and Donoghue (1996, 2001, 1996), and have since continued to be reported in recent papers (Burton 2015, 2012). This raises the question as to what strategy needs to be adopted in order to deal with this problem.

The Hampshire Depression project has demonstrated that GPs do not tend to follow guidelines. This demonstrated that there was no improvement in depression treatment outcomes, despite a training program for GPs

and written guidelines (Thompson 2000). The WHO ICD-10 GP treatment guidelines also have been shown not to have influence on GP treatment (Croudace 2003, Upton 1999).

SUGGESTED SOLUTIONS

Tylee has suggested and implemented a project where by GP leaders are trained to offer help to GP practices in order to enable them to deal with their problems in treating Mental Health patients, and that this would include improving the treatment of Depression in practices as part of the program (Tylee 1999).

Our group have in the past recommended that structured clinics run by both GPs and practice nurses, who would act as case managers to improve concordance with treatment (Paykel 1992, Agius 2007) and ensure that patients are followed up regularly-at least once a month, for the six months of treatment for a depressive episode recommended by Paykel & Priest (1992).

The possibility that practice nurses could act as case managers in treatment of patients with depression was first investigated by Anthony Mann (Mann 1998). Unfortunately, in his study, while it appeared possible for nurses to be used in this way, no improvement in outcomes was shown, however more recent papers have shown that nurses are able to help improve outcomes in the treatment of depression and are acceptable to patients (Buszewicz 2016).

Such structured clinics could be involved in the QOF system, and also could be auditable to demonstrate improvement in depression outcomes.

Such structured clinics could be combined with the easy accessibility of a psychiatric consultant in order to help deal with difficult cases. This combination would amount to a shared or collaborative care system to optimise treatment of patients with depressive episodes in Primary Care (Agius 2010). This would be a very different treatment model from the simple application of guidelines to treatment of depression in primary care (Agius 2011).

CONCLUSION

On the above basis, we strongly advise the development of such structured clinics for depression management in primary care. We would expect that the implementation of such clinics, which are designed on the lines of the present Hypertention, Diabetes and Asthma clinics in primary care, should contribute substantially to the improvement in the treatment of depression in primary care in the UK.

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Shentong Wang and Katherine Alice Wilkinson carried out the research and drafted the text.

Mark Agius provided the original idea, supervised, edited and revised the text.

References

1. *Agius, M. Bedfordshire Primary Care Mental Health Guidelines. PRIMHE Resource Pack 2003.*
2. *Agius M, Biocina SM, Alptekin K, Rotstein V, Morselli P, Persaud A: Basic standards for management of patients with common mental illnesses in primary care. Psychiatr Danub 2005; 17:205-220.*
3. *Agius M, Murphy CL, Win A, Zaman R, Tavormina G. Developing primary care treatment of depression. Br J Gen Pract 2007; 57:501-2.*
4. *Agius M, Murphy CL, Zaman R. Does shared care help in the treatment of depression? Psychiatr Danub 2010; 22 Suppl 1:S18-22*
5. *Agius M, Vyas V. Differences between training GPs to manage depression in primary care and issuing them with guidelines, and a system of collaborative care in the treatment of depression between primary and secondary care. Psychiatr Danub 2011; 23 Suppl 1:S79-82.*
6. *Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C. et al. Effectiveness of antidepressants. Meta-analysis of dose-effect relationships in randomised clinical trials. The British Journal of Psychiatry 1999; 174:297-303.*
7. *Burton C, Cameron I, Anderson N: Explaining the variation between practices in the duration of new antidepressant treatment: a database cohort study in primary care. Br J Gen Pract 2015; 65.631:e114-e120.*
8. *Burton C, Anderson N, Wilde K, Simpson CR Factors associated with duration of new antidepressant treatment: analysis of a large primary care database. Br J Gen Pract. 2012; 62(595):e104-12.*
9. *Buszewicz M, Griffin M, McMahon EM, Walters K, King M Practice nurse-led proactive care for chronic depression in primary care: a randomised controlled trial. The British Journal of Psychiatry 2016; 208:374-380*
10. *Cheeta S Schifano F, Oyefeso A, Webb L, Ghodse AH. Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998–2000. The British Journal of Psychiatry 2004; 184: 41-47.*
11. *Croudace T , Evans J, Harrison G, Sharp DJ, Wilkinson E, McCann G, Spence M, Crilly C, Brindle L. Impact of the ICD-10 Primary Health Care (PHC) diagnostic and management guidelines for mental disorders on detection and outcome in primary care. The British Journal of Psychiatry 2003; 182: 20-30.*
12. *Donoghue J: Antidepressant use in primary care. In Depression: Social and Economic Timebomb. Edited by Ann Dawson and Andre Tylee BMJ Books, 2001; p151-156.*
13. *Donoghue J Tylee A Wildgust HJ: Cross sectional database analysis of antidepressant prescribing in general practice in the United Kingdom. Br J Psychiatry, 1996; 168:164-168.*

14. Donoghue JM & A Tylee: The treatment of depression: prescribing patterns of antidepressants in primary care in the UK. The British Journal of Psychiatry 1996; 168: 164-168.
15. Donovan S, Clayton A, Beeharry M, Jones S, Kirk C, Waters K, Gardner D, Faulding J, Madeley R. Deliberate self-harm and antidepressant drugs. The British Journal of Psychiatry 2000; 177.6:551-556.
16. Goldberg D. WHO guide to mental health in primary care: a guide to mental ill health in adults (2000). London: Royal Society of Medicine Press.
17. Mann AH, Blizard R, Murray J, Smith JA, Botega N, MacDonald E, Wilkinson G. An evaluation of practice nurses working with general practitioners to treat people with depression. Br J Gen Pract. 1998;48:875-9
18. NICE. Depression in adults: recognition and management NICE guidelines [CG90] Published date: October 2009 Last updated: April 2016
19. Old Age Interest Group. How long should the elderly take antidepressants? A double-blind placebo-controlled study of continuation/prophylaxis therapy with dothiepin. The Br J Psychiatry 1993; 162:175-182
20. Paykel ES & Priest RG: Recognition and management of depression in general practice: consensus statement. BMJ 1992; 305:1198.
21. Simon GE Von Korff M, Rutter CM, Peterson DA. Treatment process and outcomes for managed care patients receiving new antidepressant prescriptions from psychiatrists and primary care physicians. Archives of General Psychiatry 2001; 58: 395-401.
22. Thompson, C et al. Effects of a clinical-practice guideline and practice-based education on detection and outcome of depression in primary care: Hampshire Depression Project randomised controlled trial. The Lancet 2000; 355: 185-191.
23. Tylee, A et al. Identification of depressed patient types in the community and their treatment needs: findings from the DEPRES II (Depression Research in European Society II) Survey. International clinical psychopharmacology 1999; 14:153-166.
24. Tylee A: RCGP Mental Health Management Course Journal of Primary Care Mental Health (PRIMHE), 1999; 1:13-4.
25. Upton, MW Evans M, Goldberg DP, Sharp DJ: Evaluation of ICD-10 PHC mental health guidelines in detecting and managing depression within primary care. The British Journal of Psychiatry 1999; 175:476-482.
26. Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. Cochrane Database Syst Rev 2012 Nov 14; 11:CD006727.
27. Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. Cochrane Database Syst Rev. 2016 Sep 9; 9:CD006727.

Correspondence:
Mark Agius, MD
Department of Psychiatry, University of Cambridge
Cambridge, UK
E-mail: ma393@cam.ac.uk