Aim of these guidelines

The aim of these guidelines is to provide recommendations, evidence-based where possible, to guide primary health care professionals in their use of antidepressants in the treatment of adults with depression and for whom the agreed course of action is to prescribe an antidepressant. The relative efficacy and tolerability of the various groups of antidepressants is explored, as well as performance within groups of certain individual drugs of interest. This information is drawn together with evidence on safety and health service resource use to profile the costs and benefits of antidepressant choice. The development group assumes that health care professionals will use general medical knowledge and clinical judgement to apply guideline recommendations when managing individual patients. It is also assumed that health care professionals will note the information, contraindications, interactions and side-effects contained in the British National Formulary. Recommendations may not be appropriate for use in all circumstances. The practitioner must make decisions to adopt any particular recommendation in the light of available resources and circumstances presented by individual patients. This is a summary of the full version of the guidelines (North of England Anti-depressant Guideline Development Group, 1997). The methods of developing the guidelines have been described previously and are summarized in Table 1.

Depression caseload

The prevalence and workload of diagnosed depression in primary care can be estimated from the recent national Morbidity Survey in General Practice for England and Wales. These data indicate a prevalence in general practice of about 5% for neurotic and depressive illness, and an average of two consultations per patient per year. Patients are predominantly middle-aged and about two-thirds are women. Depression is one of the most common single reasons for attending a GP, and the majority of depressed people who receive treatment do so in primary care.

Current patterns of use of antidepressants

Antidepressants are the mainstay treatment of depression in primary care in the UK. Approximately one million person-years of treatment are currently provided annually. Volume of use is increasing; this may reflect increasing prevalence of depression, or increasing recognition of, and diagnosis and treatment with antidepressants. GPs currently spend £160 million annually on antidepressants, and this is increasing dramatically as newer (and more expensive) antidepressants become available (Fig. 1).

Using data supplied by the Prescriptions Pricing Authority (PPA), it is possible to estimate the total volume...
The search strategy

We searched the electronic databases MEDLINE and EMBASE using a combination of subject heading and free-text terms aimed at locating systematic reviews, meta-analyses, randomized trials, quality of life studies and economic studies. The search was backed up by the expert knowledge and experience of group members.

Synthesizing and describing the literature

The quality of relevant studies retrieved was assessed and, from relevant papers, the information was synthesized using meta-analysis. This provided valid estimates of treatment effects using approaches that provided results in a form that could best inform treatment recommendations.

Categories of evidence

Ia: evidence from meta-analysis of randomized controlled trials  
Ib: evidence from at least one randomized controlled trial  
IIa: evidence from at least one controlled study without randomization  
IIb: evidence from at least one other type of quasi-experimental study  
III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies  
IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Strength of recommendation

A: directly based on category I evidence  
B: directly based on category II evidence or extrapolated recommendation from category I evidence  
C: directly based on category III evidence or extrapolated recommendation from category I or II evidence  
D: directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

FIGURE 1  GP-prescribed antidepressants in England:  
cost, quarterly

FIGURE 2  GP-prescribed antidepressants in England:  
volume, quarterly

of person-years of treatment purchased using World Health Organisation Defined Daily Dose levels (Fig. 2). In total, approximately one million person-years of treatment are currently provided annually, with tricyclics providing the majority of treatment, although the balance of treatment between tricyclics and newer drugs is changing over time. It is interesting to note that the volume of use is increasing; this may reflect increasing prevalence of depression, or increasing recognition of, and diagnosis and treatment with antidepressants.
Guideline recommendations

As they represent the most cost-effective option, tricyclic antidepressants should be used as the routine first-line drug treatment for depression in primary care (C).

The choice of antidepressant should be based on individual patient factors, which would include (D): the desirability or otherwise of sedation or other effects associated with a particular drug; previous response to a particular drug; comorbid psychiatric or medical conditions; and concurrent drug therapy.

If the toxic effects of the older tricyclic antidepressants are perceived to be a problem, for example, in a patient who has previously taken a drug overdose, then lofepramine is a more cost-effective choice than an SSRI (C).

The dose of tricyclic antidepressants should be titrated up to the doses used in the clinical trials (D). Lower doses should be used initially in older patients (D).

If patient compliance is a concern, tricyclic antidepressants can be given in a once-daily dosage (D).

When faced with a patient not responding to first-line drug therapy, reasonable options are (D): review the diagnosis; check compliance with drug therapy; consider a change in drug treatment; consider the potential contribution of maintaining factors (e.g. co-morbidity, poor housing, etc.); and consider referral to a psychiatrist.

Evidence from trials

Efficacy of antidepressants

Statement: “Tricyclic antidepressants appear slightly more efficacious than SSRIs or related drugs, although this effect is of uncertain practical importance (Ia).”

Ninety-eight trials contributed data to the analysis of the relative efficacy of SSRIs and related drugs with comparator antidepressants6,8–18,20–22,25–27,30,32,34–38,40,42–44,46–48,50–53,55–60,62,64–66,68–83,85–88,90–94,96,98,99,100–102,105–113,116,117–122,124,125,128–131 (Fig. 3). Analysis of efficacy was based on 5044 patients treated with an SSRI or related drug, and 4510 treated with an alternative antidepressant. The standardized effect size for SSRIs and related drugs together versus alternative antidepressants using a fixed effects model was 0.034 (95% CI –0.007 to 0.075, Q = 149.34, d.f. = 98, P = 0.001), a small and statistically non-significant effect (P = 0.052) in favour of alternative antidepressants. This result is roughly equivalent to about one-third of a Hamilton Depression Rating Scale point.

This result was fairly robust to the assumptions on inclusion: the standardized effect size for SSRIs alone compared with tricyclics was 0.030 (95% CI –0.018 to 0.092, Q = 88.64, d.f. = 66, P = 0.03). Analysis of the comparative efficacy of SSRIs and tricyclic antidepressants in in-patients (judged likely to be a more severely affected group) provided a slightly larger estimate of effect favouring tricyclic antidepressants, though again non-significant. The overall estimate of effect in this grouping of studies8,16,27,35,44,47,69,73,74,77,80,81,82,86,88,91,94,98,99,105,108,111,118,120,127 (using a random effects model) was 0.10 (95% CI –0.072 to 0.272, Q = 49.34, d.f. = 22, P = 0.008).

We undertook further analyses comparing the five SSRIs currently licensed in the UK (Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline) as a group, with individual alternative antidepressants (Fig. 4). Twenty-three trials compared an SSRI with amitriptyline,10,12,17,38,40,43,44,52,65,78,92,101,105,107–109,111,118–122,125 and 22 with imipramine.11,16,20–22,32,39,60,62,66,71,75–77,79,82,83,87,99,102,112,113 The pooled standardized effect size for SSRIs versus amitriptyline was 0.054 (95% CI –0.029 to 0.137, Q = 21.57, d.f. = 22, P = 0.49), and for SSRIs versus imipramine was –0.005 (95% CI –0.089 to 0.079, Q = 31.57, d.f. = 22, P = 0.09).
Drop-out from treatment

Statement: “SSRIs and related drugs are slightly better tolerated than tricyclic antidepressants, reducing the risk of drop out by about 4% during 6 weeks of treatment in double-blind randomised trials (Ia).”

The overall drop-out in double-blind randomized trials is multifaceted, having many explanatory factors including intolerable side-effects, lack of efficacy and improvement; hence, the preference for a random effects model. However, as a proxy measure for tolerability, overall drop-out is preferable to self-report rationales for treatment discontinuation (which in addition to multiple effects may be subject to substantial reporting bias). While overall drop-out is the best available measure of drug tolerability, it is unclear to what extent the patterns found in double-blind randomized trials may be generalized to clinical practice.

We used overall reported drop-out rates from trials as a proxy for the tolerability of antidepressants. One hundred and twenty-three trials contributed data to the analysis of premature drop-out (Fig. 5). The median range of follow-up was 6 weeks in the trials. Out of a total of 7032 treated with an SSRI or related drug, 1948 patients (27.7%) dropped out of a trial prematurely, compared with 2072 treated with an alternative antidepressant out of a total treated of 6334 (32.7%); relative risk 0.87 (95% CI 0.80–0.95). That is a pooled risk difference, using a random effects model, of 4.1% (95% CI 1.5–6.8%, $Q = 376.95$, d.f. = 122, $P < 0.0001$) in the absolute rate of drop-out. The results were robust to: assumptions on inclusion [the relative risk for SSRIs versus tricyclics alone was 0.88 (95% CI 0.83–0.95, $Q = 104.8$, d.f. = 86, $P = 0.08$)]; the type of model used, as similar findings were obtained for both analyses when a fixed effects model was used.

There are 25 trials comparing amitriptyline and SSRIs, and 30 comparing imipramine and SSRIs (Fig. 6). The relative risk, using a random effects model, for amitriptyline versus SSRIs, is 0.87 (95% CI 0.77–0.99, $Q = 28.46$, d.f. = 24, $P = 0.24$), and for imipramine versus SSRIs (using a random effects model) is 0.91 (95% CI 0.80–1.03, $Q = 45.71$, d.f. = 29, $P = 0.03$).

Effective doses of antidepressants

The trials included in the meta-analyses conducted for these guidelines appear to use higher doses of antidepressants in comparison with those perceived to be used in general practice. The relative severity of patients in the trials which were included, coupled with the emphasis of inclusion criteria on biological symptoms, precludes the general conclusion that doses found to be effective in the trials are required in primary care. One pragmatically designed, unblinded trial was located comparing the efficacy of fluoxetine with imipramine or desipramine in the US. Patients who were included in the trial were, on average, substantially less severely depressed than those in the double-blind trials. We found no good evidence to support the extrapolation of higher doses to primary care, or the relationship between choice of antidepressant, dose and quality of life. However, in patients that do not respond to lower doses, or whose symptoms are particularly severe, titration to higher doses is recommended.

Second-line treatment

The guidelines group felt that it was important to comment on appropriate second-line care, although not informed by trials, given the considerable number of patients failing to respond to first-line treatment. The recommendations listed above reflect the views of the guideline group on good practice in the light of available evidence and experience.
Safety and cost-effectiveness

Toxicity and safety of antidepressants

Statement: “There is a substantial range of toxicity associated with different antidepressants as currently used in primary care. The SSRIs and lofepramine are associated with the smallest risk of fatal poisoning (III).”

The average death rate associated with single-ingested antidepressant toxicity is 0.00034 per year of treatment. One fatality may be expected for about every 3000 patients treated for 1 year. However, tricyclic antidepressants (excluding lofepramine) have a higher associated fatality rate, approximately one fatality for every 1750 patients treated for 1 year. SSRIs as a group are relatively safe, with a group fatality rate of approximately one death for every 100,000 patients treated for 1 year. Lofepramine features a fatality rate similar to the SSRIs of approximately one death for every 59,000 patients treated for 1 year, and is not statistically significantly different from the SSRIs. The full analysis based upon 3 years of prescribing data from primary care supplied by the Prescriptions Pricing Authority and 3 years of data on poisonings derived from data supplied by the Office for National Statistics (1993–1995) is described in the full guidelines.2 The potential importance of non-fatal poisonings and the suggested link between antidepressant use and accidents are also examined in the full guidelines.2

Economics of antidepressants

Statement: “A general policy of switching from tricyclics to SSRIs does not appear cost-effective. Where the toxic effects of tricyclic antidepressants give cause for concern, substitution with lofepramine appears relatively cost-effective (III).”

Greater safety in overdose may lead to fewer hospital admissions for poisoning-related incidents. Also, careful matching of pharmacological properties to patient lifestyle (e.g. level of sedation) may reduce drug-associated accidents.

Although fatal poisoning due to tricyclic antidepressants is a rare event, hospitalization attributable to the unwanted effects of these drugs may lie between 3% and 5% per year of treatment. After considering all the differential effects between drugs, as a strategy for saving life, a general policy of switching from tricyclics to SSRIs does not appear to be cost-effective. Where there is a concern about toxicity, benefits may be achieved in a more cost-effective manner through substitution to lofepramine.

Two scenarios are presented in the full guidelines2 to explore the likely impact upon health service costs and toxicity-associated fatalities of general policies to increase the use of SSRIs or lofepramine and decrease the use of other tricyclic antidepressants. Recommendations, based on the type of modelling approach used are necessarily tentative, and consequently receive a lower-grade recommendation. The weakness of the approach can be seen in one published cost-effectiveness analysis which claimed to show that paroxetine was more cost-effective than imipramine134 and which caused considerable debate.135,136 Reworking by other analysts who revisited the key assumptions of the model led to opposite conclusions.137 One large pragmatic trial conducted in the US has attempted to resolve the issue of overall health care costs using different antidepressants.132 However, due to design limitations, its findings have no obvious interpretation in the UK setting.133,138

Further research

The guidelines development group identified the need for high-quality ‘real world’ trials in primary care to examine the relative efficiency of antidepressants in adults and the elderly.133 Current phase 3 trials, although large in number, do not examine a directly relevant population of depressed patients. Trials need to address both clinical and economic end-points, and use both a disease-specific and a generic patient outcome measure.

Acknowledgements

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