Quality use of medicines: Weighing SSRIs and TCAs

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This review was prompted by a comment on the E-DRUG list after the recent launch of the 13th World Health Organization Model Essential Medicines List.[1] The author, an Oxford academic, noted that amitriptyline remained the only listed antidepressant and expressed the view that "one of the SSRIs (selective serotonin reuptake inhibitors) should have been included because of their superiority in terms of side effects, although not in efficacy. Fluoxetine, now off patent, could be a good choice for a future EDL".[2] Amitriptyline is listed, but with a "square box" symbol, signifying that it is intended as "the example of the class for which there is best evidence for effectiveness and safety", and possibly is also "available at the lowest price, based on international drug price information sources". The intention of this review is not to examine the validity of the WHO Model List choice, but to show how it can illustrate the difficulties of weighing evidence of efficacy, safety, suitability and cost. *(SA Fam Pract 2003;45(6):46-48)*

MULTI-ATTRIBUTE UTILITY ANALYSIS

Previous papers in this Quality Use of Medicines series have attempted to combine evidence on the 4 elements (efficacy, safety, suitability and cost) used in the P-drug process in the form of a matrix – a multi-attribute utility analysis table. However, the relative weight accorded to each element has not been dealt with extensively. Scores for each element have also been represented simply – e.g. '++' being better than '+'. The WHO Guide to Good Prescribing also skims over this issue, almost implying that the four elements carry equal weight.[3] In the example used, the statement is made that "There is no evidence of a difference in efficacy and safety between the three active substances in the group. With regard to suitability, the three substances hardly differ in contraindications and possible interactions. This means that the ultimate choice depends on cost".

More extensive scoring systems have been proposed. Mathur and colleagues suggested weighted scores for efficacy, safety, cost of a course of therapy, compliance, multiple usage and storage, ease of administration and local availability as criteria for the selection of essential medicines.[4] Perhaps the most extensive system was that popularised by Janknegt and colleagues in the Netherlands – the System of Objectified Judgement Analysis (SOJA).[5] SOJA depends on a panel of experts prospectively defining the criteria to be used for a given group of drugs, as well as the relative weight to be given to each criterion. In this way, irrational factors are removed from the decision-making process – such as positive or negative emotional criteria based on personal experience with a particular medicine, or its manufacturer. The basic set of criteria includes clinical efficacy, incidence and severity of side effects, dosage frequency, drug interactions, cost, documentation (e.g. a score based on the number of double-blind comparative studies published, the number of patients in those studies as well as the number of years of experience and total number of exposed patient days for the drug), pharmacokinetics and pharmaceutical aspects. Additional criteria can then be added, such as the chance of developing resistance (in the case of antimicrobials). The key to the system is, however, the use of numerical scores. For example, dose frequency may be weighted as worth 50 points out of a total of 1000, and then scores awarded for once daily (100%), twice daily (80%), three times daily (40%) and four times daily (10%), based on anticipated patient compliance with each required regimen. However, SOJA also takes into account another factor when assigning relative weights to the criteria – the ability to discriminate. Noting that clinical efficacy comparisons between agents in the same class rarely show major differences, the authors suggested that, while efficacy is usually rated by practitioners as the most important criterion, it is "rarely a discriminating factor for drug selection". Antidepressants are a good example of this type of problem.

THE SCALE OF THE PROBLEM

Most reviews on the treatment of depression start by pointing out the growing prevalence of the condition, as well as the increasing resources devoted to its management. Two factors are at play – the volumes of antidepressants prescribed as well as the use of newer, more expensive agents. An Australian survey found that antidepressant prescribing had increased from 12.4 defined daily doses (DDD)/1000 population per day in 1990 to 35.7 DDD/1000 population per day in 1998, representing an increase from 5.1 million to 8.2 million prescriptions.[6] This was largely due to a rapid growth in the size of the SSRI market, accompanied by only a 25% reduction in the use of the older (and cheaper) tricyclic antidepressants (TCAs). TCAs represented only about 20% of DDDs prescribed (somewhat skewed by the fact that mean TCA doses were lower than the DDD, e.g. 59mg/day for amitriptyline, compared to the DDD of 75mg, whereas SSRI doses more closely approximated the DDD, e.g. 24mg/day for fluoxetine, compared to the DDD of 20mg).[7] Depression was the fourth most common problem managed in Australian general practice in 1998, with general practitioners responsible for 85% of such prescriptions. Intriguingly, more recent data has pointed to a potential problem of SSRI/TCA co-prescription in some Australian states, predominantly by psychiatrists.[8]

Although similar data for South Africa are not in the public domain, there is no reason to believe that the picture is any different. Newer antidepressants have been aggressively marketed and the trade name of at least one – Prozac® - is easily recognised by the lay public.

WEIGHING EFFICACY

Gathering evidence in this field is not easy. The volume of primary data is extensive, but so too are the number of meta-analyses and reviews. Melander *et al* have pointed to a particular problem.[9] This critical review of 42 studies submitted to the Swedish regulatory authority by applicants for registration of 5 different SSRIs revealed a worrying degree of multiple publication. The 42 studies were published in 38 different papers. However data was included in multiple publications, without this always being apparent. For example, for one of the SSRIs, 8 studies resulted in three pooled publications, based on different combinations of the data. A publication based on 2 studies (described as a "double blind comparison") appeared at the same time as one based on all 8 studies (described as a "large, multicentre study"), with only one author in common and no cross-reference. The 8-study paper was reported as a "per protocol" analysis. Later, data from 5 of these studies were presented as an "intention to treat" analysis, without revealing that 3 studies had been omitted or that 2 of the studies had appeared earlier as stand-alone publications. It is therefore critical to check that meta-analyses have excluded such multiple publications, and also to see how updates on such reviews have included new evidence.

Yet another source of potential bias was exposed by three prominent authors in this field, Barbui, Hotopf and Garattini.[10] They showed that the dose of the archetypical SSRI, fluoxetine, was higher in trials where it was the experimental drug (being compared to the existing reference antidepressant; 60 trials, in 42.9% of which the average dose was more than 30mg/day) than in trials where it was the comparator drug (served as the reference antidepressant, compared to a new agent; 43 trials, in only 12.5% of which the average dose exceeded 30mg/day). Not surprisingly, the weighted rate of fluoxetine responders was higher in the first group (experimental, higher dose).

The most recent source of high-level evidence for efficacy is an updated Cochrane review, published in 2003.[11] The measure of efficacy was based on combined data from 98 trials, including 5044 patients treated with SSRIs and 4510 with an alternative antidepressant. A negative pooled standardised mean difference (or effect size) would favour SSRIs (i.e. lie to the left of the midline on the familiar "blob-a-gram" graphical representation). In this case the effect size was 0.035 (95% confidence interval (CI) -0.006 to 0.076). As can be seen the CI includes unity (no difference). Given the small effect size, it could also be said that there were no statistically or clinically significant differences in efficacy between the two groups. This was also true if only the TCAs (as opposed to heterocyclics) were used as comparators.

This evidence is in line with previous meta-analyses. In 2000, Anderson pooled the data from 102 studies, in which 5533 patients received an SSRI and 5173 a TCA.[12] The effect size was –0.03 (95% CI –0.09 to 0.03), where a negative value favoured the TCAs. MacGillivray *et al* have argued that data from secondary care settings (e.g. including in-patients and specialist clinics) might skew such analyses, and performed a meta-analysis on 11 studies (2951 participants) done in primary care settings. No difference could be shown (effect size 0.07, 95% CI –0.02 to 0.15).[13]

Overall, it can be said therefore that TCAs have similar efficacy to SSRIs. That amitriptyline should continue to be regarded as the model agent is also supported by data presented by Barbui and Hotopf.[14] Compared to other TCAs it showed a marginal benefit in efficacy (weighted odds ratio 1.11, 95% CI 0.99-1.25), and this was also demonstrated against SSRIs (weighted odds ratio 1.14, 95% CI 0.94-1.38).

The question though is, if the evidence is unable to discriminate between the groups of antidepressants, should this not be weighted lower than other criteria, despite its importance? To what extent should the weighting be informed by the short-term nature of most trials and the use of surrogate (rating scores) rather than hard outcomes (e.g. rates of suicide)?

WEIGHING SAFETY AND SUITABILITY

Randomized controlled trials (RCTs) are poor indicators of safety, as evidence of side effects often emerges with continued use in larger numbers of patients. In the case of antidepressants, a large body of evidence is concerned with discontinuation (dropout) rates, as a marker of tolerability. However, drop-outs due to inefficacy may sometimes be included where the reasons for discontinuation are not made clear.

A 2000 Cochrane Review included data from 136 trials, and showed SSRIs to be better tolerated than other groups (odds ratio 1.21, 95% CI 1.12-1.30).[15] Dropouts due to side effects were also

different (odds ratio 1.48, 95% CI 1.32-1.66). This held true for the older (e.g. amitriptyline and imipramine) and newer tricyclics (e.g. dothiepin and lofepramine), but was not statistically significant in the case of the heterocyclic and related compounds (e.g. mianserin and bupropion). Very similar data were reported by Barbui and Hotopf in comparison to amitriptyline.[14] They showed that 13.1% more patients on amitriptyline reported side effects, compared to all other agents – put another way, for every 8 patients (95% CI 6-10) treated with amitriptyline rather than any other agent, 1 more would experience a side effect. In primary care settings, MacGillivray *et al* showed dropout rates of 11.6% with SSRIs (95% CI 9.9-13.3%) compared to 17.0% with TCAs (95% CI 14.8-19.1%). This held for newer and older tricyclics, but they noted that the doses of the older agents used in the trials they reviewed were relatively high. Anderson showed a more modest difference.[12] Although more patients on TCAs (31.4%) than on SSRIs (27.0%) discontinued treatment, dropouts due to side effects were responsible for only half these rates (17.3 and 12.4% respectively). This risk difference translated into a number needed to treat of 33 (95% 22-67).

However, as Trindade *et al* have pointed out, the side effect profiles of the two groups of agents is vastly different.[16] TCAs are associated with anticholinergic side effects (dry mouth, constipation, blurred vision, urinary retention, and postural hypotension). SSRIs commonly cause nausea, diarrhoea, insomnia, nervousness, agitation and anxiety. In addition to showing no difference in dropout rates (based on 84 trials), they showed that this was not affected by the means with which adverse event histories were elicited (spontaneous reporting, indirect questioning or checklists). Two subsequent letters criticised this use of meta-analysis of RCT data, as other important safety considerations were missed, such as rare but clinically important side effects and drug-drug interactions.[17,18] Different adverse effects may have quite different clinical significance in particular patient groups, such as the elderly. Yet another aspect not amenable to settling on the basis of meta-analyses of RCT data is that of the danger of the different agents in overdose. A recent Australian review showed that TCA poisoning accounted for 43% of 256 admissions due to antidepressant overdose, at one hospital emergency department over a 4-year period.[19] However, while the SSRIs were associated with some problems (in those who developed a serotonin syndrome), TCAs were associated with significantly more morbidity. There were however no deaths during the period.

Thus, while adverse effect rates vary (favouring the newer agents), how should this be weighted, given the considerable disconnect between trial and practice conditions? How can different types of side effects be compared, and the rare occurrence of potentially life-threatening problems be accommodated?

WEIGHING COST

Many economic studies have attempted to offset the higher cost of the SSRIs with predictions of lower overall costs, due to lower discontinuation rates.[20] However, as Valeria Frighi pointed out on E-DRUG, the economics of the matter has been altered by the entry of generic versions of fluoxetine, the first SSRI. In South Africa, while the retail cost of the branded original is in the order of R412 (for 30 of the 20mg capsules), six generic versions are available, ranging from R109 to R137. Other SSRIs are clustered in the R376 to R447 range. Interestingly, the original branded amitriptyline is similar in price to the branded SSRIs (R414 for 100 of the 25mg tablets), while generics are available for about R170.

CONCLUSION

As this review has shown, medicine selection analyses are time dependent. Evidence is continually being produced, and acquisition costs may change abruptly when patents expire. Weighting the evidence for each of the criteria used, whether the minimal P-drug list or more extensive sets, should take into account not only the importance of the criterion, but also the ability of the data to discriminate between the various options. In this case, data on efficacy shows little difference, crude occurrence rates of side effects are difficult to compare when the side effects are so different, but discontinuation rates do somewhat favour one group over another. Hard measures of suitability issues are almost impossible to find, leaving cost as the major discriminant. Weighting efficacy heavily will result in an outcome that supports that of the WHO Expert Committee, whereas local cost data seem to indicate that SSRIs (also being better tolerated) should also be available. However, just as a judgement call is always necessary in such analyses, so clinical judgement will have to be exercised in choosing the best agent for the individual patient.

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Please refer to the CPD questionnaire on page 53.

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