2nd SESSION

New Antidepressants for Older People: A Critical Review of the Evidence Base

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I am going to talk, as Professor Jalenques said, about antidepressants in older people. I was very pleased to be reminded of what I had written in 1995, when I thought that things were very simple. I thought that new antidepressants were much better and that is all there was to it. What we need to ask ourselves now is whether, with all the new evidence now available, we can still make the same statements with the same degree of confidence.

What I am going to try and do in the time available to me is first of all to talk a little about what I think we all share. We all share an interest in depression in older people, and one reason for that is that this is a common, important and disabling problem. Therefore, I will talk a little bit about that. I will then move to the evidence, particularly the evidence from randomised controlled trials. Most of what I am going to be talking about is acute trials, but I will also talk just a little bit, for completeness, about refractory depression. Perhaps more importantly, I will talk a little bit about longer-term studies, studies of continuation treatment to prevent relapse and of maintenance treatment to prevent or recurrence.

What I will not be talking about is depression in the context of dementia. This has been the subject of much of the discussion earlier today and will continue to be much of the discussion for the rest of the day. However, I think that is perhaps a wise omission, given that other distinguished speakers will be covering these aspects. Then finally, I will try and bring what I have said to some useful conclusions.

I said I would start by talking about the scale of the problem, and will begin by referring to a study that I am sure most of you are familiar with. This is the EURODEP study [1] and took place in a number of sites, mainly cities, across Europe. There are really two points that I want to make from EURODEP. One is that there are variations in depression prevalence between these European sites, but I would argue that those variations are not really so important. What is more important is the similarity of the pattern that you see across Europe and which can also be seen in other studies across the world. On average, about 13-14% of older people, of people over the age of 65 have sufficient depression to be diagnosed a case, and for it to be quite clearly reasonable to think about treatment. However, we must not forget that there are also the people with significant and sometimes quite disabling symptoms of depression, but who do not have a sufficient range of symptoms or a sufficient number of symptoms to justify them being diagnosed as a case of depression. They are about the same percentage again. Significant depression is thus very common in older people, but it is far from being a normal part of the ageing process.

A study that I was involved in some years ago [6] tried to quantify the cost of health and social care utilisation in a representative sample of people aged 65 and over, living in the community. People with significant physical illness, with limitation in activities in daily living, used more than three times as much service as people who were well. People with dementia, the subject of much of your discussions today, used the most service of all; they used more than five times as much.

However, this study also showed that people with depression and also people with anxiety used significantly more service, about 2.5 times more than people who were...
well. What is perhaps more interesting is that when we did a multi-variate (logistic regression) analysis, we found that even when we allowed for other factors, depression remained an independent predictor of high service use.

Another reason why depression is important is because of its prognosis. Studies following up community-identified cohorts of older people with depression were summarised by my group [9]. Overall, only about half were free of depression at follow-up; the remainder had either remained depressed or developed a recurrence. Most of the studies also reported that the mortality was also much higher than expected for such a population.

One of the problems with depression in older people is under-treatment. We found, in a more recent epidemiological study in Islington, that although people with depression were more likely to be receiving psychotropic drugs than the people who were well, only 13% were receiving an antidepressant [10]. The overwhelming majority of older people in the community with depression are still not receiving antidepressant drugs. It is also true in younger adults that a great many do not receive treatment, but these figures are much more striking than what one finds in most studies in younger people.

Why is it that older people do not receive the treatment that might be helpful? I reviewed this question a few years ago [7]. First of all, there are some problems with the diagnosis of depression in older people. Many symptoms that form part of the depressive symptom cluster may occur in older people for reasons other than depression. Older people may for example be preoccupied because of their recent experiences with thoughts of death, their own death and the death of others. They may experience excessive fatigue for physical reasons. They may experience changes in sexual interest and changes in sleep pattern which are part of the ageing process, rather than part of depression. However, changes in sexual interest and changes in sleep occurring over a short period of a few weeks or a few months, remain quite good indicators of depression in older people.

There are also some differences in symptom pattern. In particular, older people are less likely to complain of low mood. That is one of the reasons why they are less likely to fulfil standard diagnostic criteria for major depression. On the other hand, they have more anxiety symptoms mixed with their depression. They tend to have more bodily complaints such as aches and pains. They complain of more sleep disturbance as part of their depression. Although they tend not to talk about suicide, the link between depression and actual suicide in old age is much closer than it is earlier in life. Therefore, diagnostic factors may be one important element in under-treatment.

However, diagnostic difficulties are not the only issue. We also need to remember that older people and those around them may not realise that what is happening is depression. Even if they recognise the depression, they may not recognise that it is treatable. They may have symptoms of which they feel ashamed. In particular, guilt feelings and thoughts about suicide may be things that older people are very reluctant to talk about. It may be much easier to talk about bodily symptoms, particularly when talking to a general practitioner or physician.

We, as clinicians working with older people, may ourselves be partly responsible. We may hold a whole range of ageist beliefs. We may be frightened of our own approaching old age, and think that old age is a time of multiple adversity, multiple loss; that it is a time when misery is inevitable. We may feel that older people cannot change their ways of thinking and therefore that psychological treatments will be ineffective. We may think that older people are so frail and are taking so many other medications that it is not safe to give them antidepressants. However, in fact, both for psychological treatments and the evidence base for antidepressants is really quite good. There is however a wide range of treatments that are effective in older people; these include the antidepressant drugs on which I will focus in the rest of this presentation.

What I want to do now is talk about what I said I would in the beginning, and what my title suggests I should talk about, which is the evidence base for antidepressants in older people. Ken Wilson, whom you heard, I think, speaking this morning, was the lead author, back in 2001, of a Cochrane review of antidepressants in older people [20]. What were the conclusions of that review? One can summarise the conclusions in terms of Numbers Needed to Treat (NNT); this is a useful way of comparing evidence for a range of drugs. The idea is to compare how many people you would need to treat with one treatment compared with another, in order for one extra person to benefit. For the older tricyclic antidepressants, the number was about four. For monoamine oxidase inhibitors (MAOIs) it was even lower than that. MAOIs really appear to be extremely effective drugs in older depressed patients.

What is perhaps more surprising is that for the Selective Serotonin Reuptake Inhibitors (SSRIs), which are now the most commonly used antidepressants for older people, the number needed to treat was very much higher. However, that is in fact a misleading result because there was only one study of an SSRI which was of sufficient quality to get into the analysis. That was a very large study of fluoxetine, which was only borderline significant.

What has happened since that Cochrane review? A very useful review article by Taylor and Doraiswamy [18] reported on a systematic review of all the placebo-controlled trials of antidepressants in older people. The authors were a little more permissive in their entry criteria. They allowed more studies to form part of their analysis. They identified 18 studies which met their entry criteria. They were not perfect antidepressants, but were considered by the authors to be good enough to look at in detail. 12 included a tricyclic antidepressant, five, an SSRI, two bupropion* and one mirtazapine. Those of you who did not eat too much and are not too sleepy will notice that 12 plus five plus two plus one is more than 18. That is because some of these studies had three arms, not just two!

Overall, Taylor and Doraiswami [1] concluded that these studies were sometimes relatively short; the mean duration being only seven weeks. The sample size in many of these studies was also quite small. Overall it was fairly clear that
in the majority of studies, the active drug was superior to placebo. However, the response rate to placebo was quite high and that is a story that you will probably be familiar with from studies in younger people as well. There is an increasing trend for high placebo response rate in antidepressant trials.

In summary, they found that the numbers needed to treat (NNTs) were 5 for tricyclic antidepressants, 8 for SSRIs and 7 overall. The other point they made was that it is problematic to extrapolate from these studies into the general older population, partly because many of the subjects in these studies were only a little bit over 65; they were mainly ‘young-old’. Perhaps more important, they needed to be very well physically in order to be eligible to enter the studies. In the real world in which we practise, we have to make decisions about treating older people who do have co-morbid physical conditions.

What has happened since the Taylor and Doraiswamy review? Are there other studies that help us in making clinical decisions? How much has the evidence base increased?

One new study [11] compared two formulations of paroxetine* (normal and sustained-release) against placebo. The mean age in this study was relatively high at 70, and all subjects DSMIV criteria for major depressive disorder. In the placebo group, the final Hamilton score was 12.6. 52% had a response (50% or greater improvement in Hamilton score). How does that compare with those on active treatment? In terms of response rate, it was greater in the paroxetine group, 65% and 72%. That difference was somewhat more striking for the remission rate (final Hamilton score < 8) which was 43% and 44% in the two paroxetine arms against only 26% for placebo.

A very large study compared sertraline and placebo [16]. Treatment was given for eight weeks, and the mean age was reasonably high. All the subjects fulfilled DSM-IV criteria for major depression. There was a difference in adverse-events related discontinuation; it was only 2% on placebo versus 8% on sertraline*. As for outcome, you can see that there was a rather modest advantage for sertraline. In terms of Clinical Global Impression (CGI) response, it was 45% against 35%, and in terms of the Hamilton scale, 35% versus 26%.

Next is a very recently published study from the American Journal of Psychiatry [15] of the Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) venlafaxine* against an SSRI (fluoxetine*) and placebo in unipolar non-psychotic depression. It included a large sample, 300 subjects, but there was a very high drop-out rate, with only 210/300 completing the study. Adverse-events related discontinuations were very high in the venlafaxine group, quite high in the fluoxetine group and lowest in the placebo group. As for antidepressant response, there was no difference whatever between the three groups. They did just as well on placebo, on fluoxetine and on venlafaxine. Therefore, despite the fact that this was a very well-designed and adequately powered study, it failed to find a difference, or even a credible trend. A similar negative finding was recently reported by Kasper et al. [5] who compared escitalopram* with placebo.

I want to turn now to another study of an SNRI, duloxetine*, against placebo [12]. Subjects had a mean age of 73, so it was a properly old sample. It included about 300 subjects and had a slightly unusual design in that two-thirds were on the active drug, one-third on placebo.

The first surprising thing is that adverse-events related discontinuations did not differ between the two groups: 9.7% in the duloxetine group, 8.7% on placebo. If you look at response and remission, you can see that there were statistically significant differences for both. 37% responded to duloxetine against only 19% for placebo. These are low rates for both treatment groups, but nonetheless a very clear difference. Duloxetine was also clearly superior in terms of remission rates (27% against 15%), and for cognitive outcomes. There was no difference in discontinuation rates or discontinuation-related adverse events. Duloxetine was associated with more dry mouth, nausea and diarrhoea, but these only very seldom caused discontinuation. There were minimal effects on blood pressure and pulse and on blood chemistry.

There is also some placebo-controlled evidence in refractory depression. Sunderland et al. [17] conducted a study with a Type B selective Monoamine Oxidase Inhibitor (MAOI), selegiline*. This trial had small numbers, a relatively young-old group and a cross-over design. There was a 50% response rate to selegiline, with a mean Hamilton score reduction of 37%. The selegiline was well tolerated despite the high dose (60mg) given. It is noteworthy that at this dose selegiline is no longer MAO-B selective and has to be taken with a low tyramine diet.

What else has been tried against placebo in resistant depression? The answer is methylphenidate – not, perhaps, the drug you might think of first for older people with depression. However, wallace et al. [19] evaluated methylphenidate in a small sample of medically-ill older people who appeared to have given up, who had turned their face to the wall. A crossover design was used, with four days on methylphenidate* against four days on placebo. 13 out of the 16 subjects completed the trial. There was clear superiority for methylphenidate to placebo, with seven responding fully and three partially. The methylphenidate was well tolerated.

I want to turn now to a study comparing an SSRI against electro-convulsive therapy (ECT) in resistant depression in old age [2]. This only included subjects with rigorously defined treatment resistance (two or more failed adequate antidepressant trials). There was a dramatic difference, with a very low response to paroxetine and an extremely high response to ECT.

Finally I am going to talk very briefly about continuation and maintenance. The first study I want to consider is a 24 week continuation study of escitalopram against placebo in patients who initially achieved remission on open-label escitalopram [3]. There was a dramatic difference between the two groups, with a very low relapse rate on escitalopram and rather a high relapse rate on placebo.
A similar study design was used to compare citalopram* with placebo in maintenance treatment over two years [8]. There was early separation between the two groups, very clearly maintained over the two-year period. In the placebo group, there was a very low chance of remaining free of depression for two years, but a very good chance of remaining recurrence free for those on active maintenance treatment.

There are two important studies of the combination of antidepressant and psychotherapy against placebo in maintenance treatment of patients deemed at high risk of recurrence. The earlier of the two studies [13] compared nortriptyline* and interpersonal psychotherapy (IPT) given separately or together and with a control group attending clinics but given non active treatment. In the combination treatment group, recurrence rate was very low, whereas on no treatment at all, these were extremely high recurrence rates. The nortriptyline* alone group, particularly in those under 70, also had quite low recurrence rates. The IPT alone group had a higher recurrence rate than was seen in patients on medication but lower than found on placebo alone.

Very recently, the same group [14] have repeated their study design, this time with an SSRI (paroxetine). The results were slightly different. Paroxetine with interpersonal psychotherapy and paroxetine alone, were both associated with low recurrence rates. However, inter-personal psychotherapy alone did not appear effective in preventing recurrence.

Finally, I want to introduce the idea of collaborative care, of a complex treatment package, rather than simply an antidepressant. The IMPACT study [4] is a very large, and well-designed study that involved nearly 2,000 patients aged 60 and over, treated in a primary-care setting for 12 months and then followed up for a further two years. The package involved antidepressants, but the randomisation was to the package as a whole, within which clinicians had discretion, as to what treatment was given.

The collaborative care package was associated with higher likelihood of use of an antidepressant. There was a higher likelihood of use of either antidepressant or psychological treatment. However, more importantly, collaborative care was associated with improvement in terms of a very wide range of outcomes. This was not just in terms of response or remission; patients also expressed greater confidence in their ability to manage their own depression, were more satisfied with the care they received, and their quality of life was higher. I think there are a lot of lessons from this study as to how future antidepressant studies should be carried out.

In conclusion, I would argue that depression in old age is a common and all-too-often under-treated problem. Some antidepressants are clearly efficacious, although I think we need to learn the lessons from negative trials. There is rather more consistent evidence that where antidepressants have resulted in remission, continuation of those antidepressants has very substantial effect in reducing relapse and recurrence rates. Care packages may have advantages over single-modality treatment. We badly need more data in the very old and in terms of more clinically meaningful outcomes, such as quality of life.

Thank you for your attention.

Answers / Responses

Chairperson
Thank you very much for this beautiful presentation. Your paper is now open for discussion.

Dr N. Bazin
Monsieur Katona m’a précisé avant qu’il n’était pas la peine de traduire les questions. Il les prend directement en français et vous répondez en anglais.

Dr Fabre
Dans l’étude de Schatzberg, vous avez indiqué qu’il n’y avait pas de différence entre la venlafaxine comparée à la paroxétine. Pouvez-vous nous préciser les doses employées pour la venlafaxine?

Pr C. Katona
To be honest, I cannot remember the dose. If I remember rightly, it was 75mg daily, but I may be wrong there and I do not have the paper with me. I think that is an important question, because inadequate dose is important. In older people, there is a more difficult balance between avoiding doses that are too high, particularly with a drug like venlafaxine. This may have effects on blood pressure which may be more dangerous in older people. This must be weighed against giving inadequate doses, which in some ways is worse than giving nothing at all. Therefore, I think it is a very good question and I am embarrassed that I cannot remember the exact answer.

Une intervenante
Dans cette même étude, qui est quand même assez négative dans ses résultats, ils utilisent le Hamilton pour juger de l’efficacité de l’antidépresseur. Pensez-vous que c’est une raison qui pourrait expliquer cette absence de résultat qui est quand même en contradiction avec d’autres études?

Pr C. Katona
What a wonderful question. Back in 1995, when I was able to say such clear things about new antidepressants, I also used to say very clear things about the Hamilton scale. What I used to say was that the Hamilton scale was a very bad scale in older people because it had so many somatic items which are misleading in older people. Now, I no longer say this.

Why do I no longer say it? I no longer say it because there is increasing evidence that older people very often do have painful symptoms, and somatic symptoms in general which relate closely to their depression. One cannot really make a good Cartesian divide between the bodily symptoms and the depression. Therefore, may be the Hamilton scale is not so bad after all. The other thing about the Hamilton scale is that it is very widely used. It makes it easier to compare between one study and another.

Un intervenant
A propos des études, vous montrez qu’il y a un écart relativement faible entre la réponse au traitement et la réponse placebo. Une des explications ne pourrait-elle pas venir de la brièveté des études qui sont sur huit semaines? On dit - vous commenterez peut-être - que chez les gens âgés, la réponse aux antidépresseifs peut être plus longue.
La proximité placebo au traitement n’est-elle pas expli-
cable par cela. Par ailleurs, vaut-il mieux aller vivre en
Islande ? J’ai vu que sur vos diapositives, il y avait une dif-
férence énorme entre le diagnostic de dépression, qu’elle
soit ou non caractérisée, et ce que l’on trouve à Londres ?
Quelle explication avez-vous ?

Pr C. Katona

I will take those questions in reverse order; firstly, differ-
ences between depression rates in Iceland and the UK. I
think that what one has to remember is that there are big
area bars for each of the individual cities. I am not sure
how real those differences are, and I think part of the ex-
planation may be in terms of the instruments used and the
problèmes in translation. Part of it may be that Iceland is
a very happy place in which older people are valued and
where there is a very good health service. Why there is a
higher rate in London is more difficult. I personally think
that London is also a happy place! Having said that, I think
your other question is very important, and that is about
possible explanations for high placebo response rate. Your
suggested explanation is that it is partly because the trials
were too short and treatment effects take longer to emerge
in older people. Most studies do indeed suggest that, and I
think you may well be right.

There certainly is evidence, not only in older people, that
if one continues an antidepressant trial for eight, 10, 12,
14 weeks, there is an emergent further response rates.
Therefore, I think that may be part of the explanation. I
think there are other important factors as well. Perhaps
one factor is that there has been a change in the type of
patients entered into clinical trials over the years, and
in particular, many trials now take place in primary care,
rather than secondary care.

Many trials are of people who have relatively low sever-
ity scores to begin with. There is quite good evidence that
where the depression is mild, it is much more difficult
to show a difference between active drug and placebo.
Therefore, I think the high placebo effect is not entirely age
related; you find it in younger people too. It is multi-facto-
rial, but I am sure you are right, that short duration is one
of the factors involved.

Un intervenant

Je suis souvent surpris entre les essais cliniques qui mon-
trent un faible effet indésirable avec la plupart des anti-
dépresseurs, et les réalités cliniques. Les patients que nous
soignons, sont des patients âgés, polypathologiques, poly-
médicamenteux. En gériatrie, l’un des problèmes majeurs
avec les antidépresseurs, ce sont des problèmes de sudation
excessive et de chute, et également des problèmes d’hypotonatrème. Dans ces études, on ne voit pas toute
cette réalité. Souvent, ce sont des populations de patients
ciblés, sélectionnés qui ne reflètent pas la réalité théra-
péutique et la réalité de la prise en charge clinique.

Pr C. Katona

I think that absolutely right. I think it is the biggest prob-
lem in making good use of the clinical trial evidence base.
Those people included in clinical trials are not the same as
the people we have to treat in practice. I am not sure to
what extent that is a good explanation for the high placebo
response and the small difference. However, whether it ex-
plains it or not, I think one still has the problem which you
describe, which is that the world of clinical trials is not the
same as the world of practice.

I think we should be making more of an effort to make the
clinical trial evidence base more like real life. That is why I think
that study designs of complex interventions like the impact
study may be very important signals for the future. In real
life, we do not give a single treatment compared with a
placebo. In real life, we are likely to give psychotherapy as
well as antidepressants and so on.

Une intervenante

Que pensez-vous de ces dépressions subsyndromiques dont
vous avez parlé ? Ne pensez-vous pas que cela pourrait
être des critères diagnostiques qui seraient beaucoup plus
performants que le DSM pour le sujet âgés ? Devrions-nous
utiliser cela plus fréquemment dans les essais théräpeu-
tiques ? Comme le soulignait Monsieur, ils sont vraiment
très loin de notre pratique quotidienne.

Pr C. Katona

I think that that is a very important question. I think there
are a lot of people who we as clinicians recognise as having
significant and treatable depression but who are not picked
up as major depression by standard diagnostic criteria. I
think there are diagnostic systems that work better. For
example, the Geriatric Mental Status (GMS) interview (as
used in the EURODEP studies), has a very good algorithm
for identifying people with caseness depression. Having said
that, clinical trials have not been done in that population
and we do not know with the same degree of confidence
that antidepressants are effective in such people.

Références

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