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Ken Gillman MD, MRCPsych, PsychoTropical Research, PO Box 86 Bucasia 4750, Mackay, Queensland, Australia. Email: kg@matilda.net.au

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Authors' reply

Some of Dr Gillman's trenchant criticisms arise from an apparent misunderstanding over the type of article we have written. Therefore we thought it helpful to give some background to the nature of the article before responding to the individual critiques.

The remit of the article was to review the efficacy and side-effect burden of antidepressant combinations reported in the clinical literature. Therefore, exploring specific pharmacokinetic aspects of each combination is outside the scope of this work, although we have highlighted important pharmacodynamic rationales for the combinations wherever possible. We welcome the addition of more references from Dr Gillman but we must emphasise that our original article was constrained by the limits of the journal style. *Advances in Psychiatric Treatment* is an aid for CPD that publishes reviews rather than detailed data papers and requires only a limited reference list that is accessible to readers. In many instances we therefore used secondary references that discuss the primary data papers. As indicated in the article, a fuller list of references is available on request. Table 1 contains no references but the data in it are taken from references listed throughout the review.

In keeping with the objectives of this journal a section of self-assessment follows every article. This self-assessment exercise should be in line with the Royal College of Psychiatrist's Membership Examination as closely as possible. The MCQs that follow our article are in the 'best of five' format. The reader chooses the best of five responses and this does not mean that the other responses are necessarily wrong.

Turning to the specifics, we first of all apologise for the error in copy-editing rightly pointed out by Dr Gillman. The text discussing SSRIs and TCA combinations should read 'NA:5HT reuptake blockade' and not 'sodium:5HT reuptake blockade'. We also stand corrected with the numbers reported in the SSRI/RIMA section. It should read 'Two small open-label trials (total $n=61$)'.

The effectiveness of a drug in randomised controlled trials (RCTs) is a different domain from assessing the pharmacodynamics and pharmacokinetics of compounds in the laboratory. We wish to underline the weaknesses of Nelson's RCT evaluating the desipramine and fluoxetine combination (Nelson 2004). First, the sample size was very small (39 participants, 1 of whom dropped out and another was excluded) and second, the baseline Montgomery-Åsberg Depression Rating Scale (MADRS) scores were lower in the combined treatment group (which nearly reached significance at $P=0.07$). This trial did not show a significant difference between the groups when the endpoint MADRS scores were compared. Although the mean percentage change in MADRS was numerically higher in the combined treatment group, this again failed to reach statistical significance. When categorical levels of treatment response were considered, the percentages of remitters in this 6-week follow-up trial were 54% for the combined treatment, 7% for fluoxetine and 0% for desipramine. However, when all responders (total achieving categorical remission + categorical response) are considered, the combined treatment was only marginally better (8 out of 13 in the combined group *v.* 6 out of 14 in the fluoxetine group). The percentage of 'non-responders' in the

study (5 out of 13 receiving combined treatment and 7 out of 14 taking fluoxetine) shows no statistical difference. Furthermore, Fava *et al* (1994, 2002), did not report a significant difference between high-dose fluoxetine (40–60 mg) and a fluoxetine + desipramine combination. Thus, Dr Gillman's assertion that a 'true SNRI effect' is achieved by a combination of tricyclics and SSRIs and that this results in a significant clinical advantage is at best debatable. Dr Gillman claims that we have misquoted the Nelson references regarding the speed of onset. However, it is clear from their text that the speed of onset effect they found in their earlier trial (published in 1991) was not replicated in the 2004 study. The report on the latter study (Nelson 2004) states that 'Rapid response, at 1 or 2 weeks, was neither statistically nor meaningfully greater with combined treatment'.

Moving away from Nelson's non-replicated small RCTs and looking at more meta-analytic literature might throw further light on the issues. Treatment with dual-action antidepressant drugs is more likely to result in clinical response than treatment with the SSRIs, albeit at a modest level (Papakostas 2008). Dr Gillman rejects venlafaxine being termed an SNRI in the first place. Although a detailed discussion of transporter blockade ratio and affinity is far from the original objectives of our clinically oriented narrative review, we are surprised by Dr Gillman's arguments with regard to venlafaxine. His conclusion that the SNRI effect of venlafaxine 'is closer to myth than reality' follows the statement 'venlafaxine has approximately a 200:1 differential between 5-HT:NA transporter affinity'. Using the K_i Database of the National Institute of Mental Health's Psychoactive Drug Screening Program (http://pdsp.med.unc.edu/pdsp.php), the average affinity for venlafaxine is 79 nM for human cloned 5-HT transporter (SERT) and the average affinity at the human cloned noradrenaline transporter (NET) is 2094 nM, giving a ratio of nearly 27:1 for SERT:NET affinity. In a direct head-to-head comparison, Bymaster *et al* (2001) concluded the K_i ratio for venlafaxine at human SERT and NET transporters to be 30:1. Binding affinity may not always correspond to uptake inhibition and in fact when one considers uptake inhibition assays in addition to transporter binding, this K_i ratio narrows. Vaishnavi *et al* (2004) found a SERT:NET uptake inhibition K_i ratio of around 10 for venlafaxine. Undoubtedly, the K_i ratio is only a part of the story when considering a drug's effectiveness in a clinical context; availability of the drug molecule at the site of action and proportion of target sites occupied by the drug molecule in the brain (occupancy rate) are of vital importance. Meyer *et al* (2004) used positron emission tomography (PET) to demonstrate 80% occupancy of striatal SERT at 4 weeks after starting venlafaxine at the minimum therapeutic dose of 75 mg. The SERT occupancy at minimum therapeutic doses of four different SSRIs was also approximately 80% in this study and this plateaued at high plasma levels or doses for all five compounds examined. So the therapeutic advantage shown by higher doses of venlafaxine cannot be explained solely by SERT occupancy. On the basis of K_i ratios, Dr Gillman suggests that one requires 10 times the maximum dose of venlafaxine to see clinically useful effects on noradrenergic transmission. However, *in vivo* data suggest a noradrenergic effect for venlafaxine at doses within the 'therapeutic range' – it produces tyramine pressor response at 225 mg and 375 mg in patients with depression (Debonnel 2007) and at 375 mg in healthy volunteers (Harvey 2000). Furthermore, the increased pupillary dilatation and prolonged reflex latency found in healthy volunteers on 150 mg venlafaxine has been attributed to a central noradrenergic effect (Bitsios 1999).

Dr Gillman's advocacy for venlafaxine and reboxetine combination on the basis of the 'floor effect' of venlafaxine requires further consideration. It is relevant to consider the extent of NET inhibition required for clinically meaningful effects. Unfortunately, there are no established PET ligands for the NET to address this issue. Using the discrepancy noted between SERT occupancy rates *ex vivo* and in PET studies (Owens 2008), Blier (2008) indirectly estimated NET occupancy rates for 225 mg venlafaxine to be around 70%. If venlafaxine, considered by Dr Gillman to be an 'extremely weak NRI' that cannot produce a clinically meaningful NRI effect, is able to produce 70% NET occupancy at 225 mg, then a 'true SNRI' must be producing very high occupancy levels defying logic. Thus, while we concur with the point made by Dr Gillman that venlafaxine is a weaker NRI than TCAs or reboxetine, we consider that dismissing venlafaxine's noradrenergic effects on the sole basis of transporter occupancy rates is not warranted. In fact, a growing body of literature suggests that monoamine transporters may not be as selective as once thought (Daws 2009), adding more reasons to be circumspect when translating affinity values to clinical practice.

With respect to the moclobemide and SSRI combination, we agree that we could have emphasised the risk of using this combination in more detail, but we did highlight the need for caution in using it by clearly stating that 'Despite being a reversible inhibitor of monoamine oxidase A, moclobemide can cause life-threatening serotonin toxicity'.

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Dr Gillman asserts that poor metabolisers are not at increased risk from SSRIs and TCA combinations compared with efficient metabolisers. We do not agree with this. Albers *et al* (1996) cite Alvan *et al* (1990) and report that 'Poor metabolizers of sparteine or debrisoquine, who account for approximately 7% of the Caucasian population, lack CYP2D6 and rely on a number of available lower affinity P450 enzymes to catalyze this hydroxylation reaction, thus leading to much higher levels of hydroxylated TCAs and greater potential for toxicity'. In such patients, TCAs could attain a higher plasma level, irrespective of co-administration of SSRIs. Thus, poor metabolisers are much more prone to TCA toxicity because of the high levels of plasma tricyclics (Ingelman-Sundberg 2005). It is worth noting that our review has highlighted some of the potential side-effects of using combination therapies in clinical practice; not all of these side-effects are the results of specific pharmacokinetic interactions.

In summary, we welcome the debate on these topics raised by Dr Gillman but stand by the vast majority of statements we made in the article. What is clear from this exchange is that we lack a number of things. First, we have insufficient clinical data on combinations to inform our judgements on the choice of these combinations. Second, there is a gap in working out which elements of the pharmacology of antidepressant drugs are linked to clinical response and we lack biological markers of these pharmacological mechanisms in patients.

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Lena Palaniyappan Clinical Lecturer, Division of Psychiatry, Queen's Medical Centre, Nottingham; **Lisa Insole** Consultant Psychiatrist, Northumberland, Tyne and Wear NHS Trust, St Nicholas Hospital, Gosforth, Newcastle; **Nicol Ferrier** Professor of Psychiatry, Institute of Neuroscience, Newcastle University, Leazes Wing, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK. Email: i.n.ferrier@ncl.ac.uk

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