

CORRESPONDENCE

Combining antidepressants: understanding drug interactions is the *sine qua non*

I am concerned that Palaniyappan *et al*'s review of combining antidepressants (Palaniyappan 2009) contains imprecise generalisations, inaccuracies and misquotation of references.

The introduction states 'we review the nature and extent of the side-effect burden and potential risks of these combinations'. That should entail a clear exposition of pharmacodynamic and pharmacokinetic drug–drug interactions, which are the heart of the issue. Yet these two key words (and discussion of the important concepts associated with them) do not appear in Palaniyappan *et al*'s text.

Combinations of different antidepressants are either implicitly or explicitly proscribed by various reviews and 'authorities', often the same ones who, as in this instance, get important basic facts wrong and cite references inappropriately (including mine: Gillman 2006). This is a subject about which there is already more misinformation in psychiatry texts (and in the *British National Formulary*) than you can shake a stick at: Palaniyappan *et al*'s review adds to it.

I will begin by suggesting some resources that readers may access, because, without understanding the pharmacodynamics and pharmacokinetics of interactions, they will never become confident about what to do and what not to do. My own work includes a review detailing the properties, receptor potencies, cytochrome P450 (CYP450) enzyme inhibition potencies and pharmacokinetic interactions of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) (Gillman 2007); and a detailed analysis of the pharmacodynamic interaction of serotonin toxicity, explaining which MAOIs and other drugs can precipitate it (Gillman 2006). Preskorn's major review of interactions (Preskorn 2006) is highly recommended, as are his website (www.preskorn.com) and that of Flockhart (<http://medicine.iupui.edu/clinpharm/ddis>) and the Allele Nomenclature Committee (www.cypalleles.ki.se). Most other web sources and software programs are inaccurate. Other key papers on CYP450 enzymes are: Brosen 2004; Ingelman-Sundberg 2005a,b; Sim 2006.

It is also notable that there are great differences between tranylcypromine (TCP) and phenelzine (PLZ), especially with regard to CYP450 interactions (Holt 2004): briefly, PLZ is a mechanism-based (i.e. irreversible) inhibitor of most CYP450 enzymes, whereas TCP is not, except for nanomolar (reversible) potency for CYP2A6 inhibition

(Draper 1997). These differences affect potential interactions.

Palaniyappan *et al* cite my review of the TCAs (Gillman 2007) but seem to disregard most of its content and produce an unreferenced interaction table out of step with that (and other) sources. They state, concerning my comments on dual action strategies: 'The combination of a predominantly noradrenergic TCA such as nortriptyline and an SSRI may overcome this ceiling effect and produce a different sodium:5-HT reuptake blockade ratio. However, there is no evidence that this ratio is related in any way to clinical effectiveness.'

Aside from the rendering of 'NA:5-HT' as 'sodium:5-HT', the quote indicates a misunderstanding of what I discussed, which had nothing to do with ceiling effects. Quite the opposite in fact: I argued that most SNRIs, but particularly venlafaxine, exhibit a subtherapeutic noradrenergic effect, as evidenced by low affinity at the human cloned noradrenaline transporter, and no substantial effect on the tyramine pressor response (Blier 2007; Debonnel 2007) – a 'floor' effect perhaps? Therefore, if it were possible to attain full noradrenaline reuptake inhibition, the dose required would be about 10 times the maximum dose of 300 mg, i.e. a toxic level (Whyte 2003). In fact, this extremely weak NRI is the rationale for adding reboxetine, to attain a more balanced SNRI effect. So their comment (regarding venlafaxine + reboxetine) is wrong: 'Any synergism of such a combination is doubtful, as both drugs act via the same mechanism; the same effects could be achieved by a higher dose of venlafaxine alone, with more predictable pharmacokinetics' – indeed, predictably toxic.

Also, their claim that 'there is no evidence that this ratio is related in any way to clinical effectiveness' denies the established reality, logic and basic pharmacology of the dose–response curve. Since venlafaxine has approximately a 200:1 differential between 5-HT:NA transporter affinity it is impossible to have an optimum therapeutic: side-effect ratio for both systems simultaneously, or even any meaningful balanced effect on both systems simultaneously. The tacit acceptance by psychiatrists of the notion that venlafaxine has an SNRI effect is astonishing, because it is closer to myth than reality. Contrary to Palaniyappan *et al*'s assertion, there is both theoretical and clinical evidence that dual action (a true SNRI effect) is more effective. Nelson *et al*'s randomised controlled trial (RCT) of fluoxetine and desipramine indicated much higher remission rates at 6 weeks for combined treatment (54%) than for the SSRI (7%) or desipramine (0%) alone (Nelson 2004). Palaniyappan *et al* also misrepresent that trial by reporting: 'In any event, this speed of onset effect could not be replicated in

a later RCT (Nelson 2004)', without mentioning the remission rate. They also use this same reference a second time, implying that it is subsequent work.

Their material and references on my area of expertise, serotonin toxicity, are poor for a review article. The section headed 'SSRI with moclobemide' shows a lack of familiarity with the literature on reversible inhibitors of monoamine oxidase A (RIMAs) and SSRIs (Gillman 2006). One of several examples of this is: 'The SSRI-moclobemide combination has been tried with the same rationale as the SSRI-MAOI combination. Three small open-label trials (total $n=46$) found moclobemide to be effective in combination with SSRIs (Dodd 2005).'

Dodd, their most frequently cited reference, is another review. It is not the original source of any data. There is limited profit in one review (mis)quoting another review. Palaniyappan *et al* misrepresent the RIMA/SSRI area of research. They misreport Dodd (who cites two open-labelled studies (Joffe 1994; Hawley 1996), not three). Hawley's original report (Hawley 1996) had 50 cases (cited by Dodd, correctly), taking the total beyond their stated 46 (Table 2). They might have noted that Hawley stated, concerning adverse drug reactions, 'Many events were rated as severe. The high rate of adverse events suggests that there are clinically significant pharmacodynamic interactions between moclobemide and SSRIs' (i.e. serotonin toxicity). Note that there are two other moclobemide/SSRI papers (Bakish 1995; Ebert 1995), although Ebert was not cited by Dodd.

Why, one might ask, despite the great enthusiasm expressed by all of these authors, has nothing else been published in the subsequent decade? I sought information on this point, repeatedly, from all those authors, but only Dr Hawley ever replied (see below).

My detailed analysis of data on animal and human serotonin toxicity, and of that regarding moclobemide in particular (Gillman 2004, 2006), provides a more substantive basis for understanding the risks of combining moclobemide and SSRIs. Among other things, my review states that 'Hawley decided to stop his research because of high levels of moderately severe serotonergic side effects', i.e. incipient serotonin toxicity. Readers of Palaniyappan *et al*'s article are likely to be left with the impression that SSRI/moclobemide combinations are 'relatively safe'. That notion is seriously contentious and the contrary evidence should have been referenced and discussed. I am supposed to be an expert in serotonin toxicity and I would not be game to try it. The answer to the third MCQ question is wrong: moclobemide + SSRI definitely could cause fatal serotonin toxicity.

The format of Table 1 is unsuitable for conveying that type of data and will probably mislead and confuse many readers. It, and the associated text, has some odd material that does not promote a good understanding of pharmacology, interactions, or CYP450 enzymes, and it is less useful than other pre-existing sources and references given here. It is, inexcusably, unreferenced. The authors state (under the heading, and in the context of, combinations of an SSRI with a TCA) 'Tricyclic toxicity ... is a particular risk for the 7% of White people who lack sufficient CYP2D6 to metabolise TCAs (Albers 1996)'. This appears to be muddled thinking because that is precisely the group in whom an interaction is less of a risk, because they are already genotypic poor metabolisers and further diminution of CYP450 activity (by SSRIs) will not make them worse; such people are at increased risk of toxicity with monotherapy with TCAs. Albers is an outdated and inappropriate reference. In my opinion readers would do better to consult the following more helpful and accurate sources: Brosen 2004; Ingelman-Sundberg 2005a; Preskorn 2006; Sim 2006; Gillman 2007; Flockhart 2009; Preskorn's extensive review contains a wealth of good information.

There are various other errors in the article, which is characterised by imprecision, unhelpful generalisations and uncritical repetition of other reviews. In my opinion anyone contemplating using combinations needs to be rather better informed than they would become by reading Palaniyappan *et al*.

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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'.

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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