COMMENTARY on:

THE PREVALANCE & OUTCOME OF PARTIAL REMISSION IN DEPRESSION

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The currently conventional model of response to and remission on antidepressants outlined in the previous article on prevalence and outcome of partial remission in depression is predicated on the assumption that depression is a categorical disorder akin to a bacterial infection, with the aim of treatment being to eradicate all traces of prior infection. This model may be misleading, if only for the reason that bacterial infections are “sui generis” conditions in medicine.

A study comparing mirtazapine and fluoxetine illustrates the failings of the conventional model.[1] In this study, the superior results with mirtazapine compared to fluoxetine might be accounted for by a better response in those who respond (i.e., fewer residual symptoms) or by a greater number of responders. In fact, the data from the study make it clear that the latter interpretation is the correct one. This finding can be best explained by suggesting that antidepressants that act on different neural systems can recruit responses from individuals of different constitutional types. Such an interpretation is consistent with a body of research, such as the study by Joyce and colleagues, indicating that the prior personality of the individual predicts outcome with selective antidepressants.[2]

In a recent study, the findings of Joyce and colleagues regarding personality were replicated in a population of healthy volunteers taking selective agents.[3] [4] The relevance of a healthy volunteer population to the issue of residual symptoms is as follows. If current treatment guidelines are followed, then the greatest amount of time any patient will spend on treatment will be in a remitted rather than a symptomatic state. If the patient’s constitutional type is such that he or she is unable to achieve significant well-

being on the primary therapeutic agent, the implications for residual symptoms becomes clear. This is precisely the scenario that data from healthy volunteer studies point to, with the additional complication that the deleterious effects of treatment may extend beyond minor decrements in levels of well-being to severe agitation or full-blown active suicidality [5] [6].

These findings in healthy volunteers are supported by evidence from a recent meta-analysis conducted by Khan et al on rates of suicide and suicidal acts on antidepressants in clinical populations. The data from the original Khan et al article have been modified in the light of an FDA Review and Evaluation of Clinical Data Original NDA 20-021, paroxetine Safety Review by Martin Brecher, June 19th 1991 and statistical reviews on sertraline, prepared for the FDA by Hilary Lee, on 8/14/1990 and 1/31/1991, which has led to a recategorisation of 2 suicides on placebo in paroxetine trials to the placebo washout period, and 3 of the 5 suicide attempts on placebo in the sertraline trials to placebo washout.

This leads to the figures in Table 1:

Table 1. Incidence of Suicides and Suicide Attempts in Worldwide Phase 1 -3 Investigational Antidepressant Clinical Trials			
Investigational Drug, Patient Randomization (Absolute Numbers.)		**Suicides, No.**	**Suicide Attempts, No.**
Sertraline hydrochloride			
Investigational drug (2053)		2	9
Active comparator (595)		0	1
Placebo (786)		0	2
Placebo Washout		0	3
Paroxetine hydrochloride			
Investigational drug (2963)		5	40
Active comparator (1151)		3	12
Placebo (554)		0	6
Placebo Washout		2	0
Nefazodone hydrochloride			
Investigational drug (3496)		9	12
Active comparator (958)		0	6
Placebo (875)		0	1
Mirtazapine			
Investigational drug (2425)		8	29
Active comparator (977)		2	5
Placebo (494)		0	3
Bupropion hydrochloride			
Investigational drug (1942)		3	----
Placebo (370)		0	----
All			
Investigational drug (12879)		27	90
Active comparator (3681)		5	25
Placebo (3079)		0	12
Placebo Washout		2	3
TOTAL (19639)		**34**	**130**

When the figures for suicides and suicidal acts on investigational drugs are calculated using patient exposure years, there are:

A-1. 842 suicides per 100,000 patient exposure years on investigational drug

B-1. 000 suicides per 100,000 patient exposure years on placebo

C-1. 3649 suicidal acts per 100,000 patient years on investigational drug

D-1. 2158 suicidal acts per 100,000 patient exposure years on placebo.

In absolute terms, the figures are:

A-2 209 suicides per 100,000 patients entered on investigational drugs

B-2 00 suicides per 100,000 patients entered on placebo.

C-2. 908 suicidal acts per 100,000 patients for investigational drugs

D-2. 389 suicidal acts per 100,000 patients in the placebo group.

The difference between new drugs and placebo for all suicidal acts reaches statistical significance at a level of $p \leq 0.05$, whether calculated as a single large trial or by adding the cumulative probabilities from each trial. .

These figures raise concerns about all these drugs, and have implications for venlafaxine, which can be considered an SSRI at commonly used doses and a dual action agent at others. The figures support the findings from healthy volunteer studies and put a premium on greater efforts to identify who will respond to which agent rather than assuming that all patients have an equal potential to respond to all agents.

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[1] Wheatley DP, van Moffaert M, Timmerman L, et al., and the Mirtazapine - Fluoxetine Study Group. Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe depressive disorder. *J Clin Psychiatry* 1998;59:306-12.

[2] Joyce PR, Mulder RT, Cloninger CR. Temperament predicts clomipramine and desipramine response in major depression. *J Affect Disord* 1994;30:35-46.

[3] Healy H, Cattell D, Tranter R, Jaffar K, Healy D. Better than well on antidepressants [abstract]. *J Psychopharmacol* 2000;14 (Suppl 3):A28.

[4] Tranter R, Healy H, Cattell D, Healy D (in press). Functional variations between agents differentially selective to noradrenergic and serotonergic systems. *Psychological Medicine.*

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[6] Saletu B, Grunberger J, Linzmayer L. On central effects of serotonin reuptake inhibitors: Quantitative EEG and psychometric studies with sertraline and zimelidine. *J Neural Transm* 1986;67:241-66.