High-dose tricyclics potentiation with mirtazapine, lithium and partial sleep-deprivation: why not tricyclics in combination strategies for resistant melancholia?

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Introduction

In recent years, combination strategies (which involve adding additional antidepressants with a different neurochemical profile) and augmentation (with nonantidepressant drugs such as lithium, T3 and atypical antipsychotics) are being used more frequently to treat resistant unipolar melancholic depression [Yazici, 2009; Blier *et al.* 2010; Ruiz-Doblado *et al.* 2010]. The use of different combination and augmentation strategies in severe, resistant depression is based clinically and physiopathologically on the neurochemical complementarity of drugs, their synergies, on the improved tolerability and reduced undesirable effects when a second drug is associated, and also on the growing body of experience with combinations of antidepressants in naturalistic conditions of 'real' clinical practice [Rush *et al.* 2009].

However, the use of the strategy of combining several drugs in resistant diseases also presents a serious predicament in other areas of medicine (e.g. high-activity antiretroviral therapy [HAART], resistant hypertension, etc.). Given that the final objective of antidepressant treatment should be complete remission of the resistant melancholia and not just a simple response, different observations have endorsed that simultaneous administration of two antidepressants may produce neurochemical changes more quickly.

Case report

A 49-year-old woman who had been admitted to hospital with severe melancholia, hypertension

on treatment and with a history of six serious melancholic episodes since she was 24 years old (first puerperium), was treated by our group. She had no previous history of mania or hypomania. The current episode, which was very severe (Beck Depression Inventory [BDI] score: 58) and had a seasonal pattern, was treated first line with a combination of venlafaxine extended release 450 mg + mirtazapine 45 mg + lamotrigine 200 mg daily, resulting in only a poor response in the fourth week (BDI score: 40). This response was manifested essentially at the BDI ITEMS which evaluates symptoms of anxiety, with a scant improvement in qualitatively specific symptoms of mood, thought, speech and psychomotor inhibition. Given the insufficient clinical response and persistence of suicidal ideas, it was decided to change the treatment to clomipramine 375 mg + mirtazapine 45 mg + lithium 800 mg daily + partial sleep deprivation. After 6 weeks, the patient achieved complete remission (BDI score: 3), with a euthymic mood, recovery of her premorbid level of functioning and complete disappearance of suicidal thoughts. It should be pointed out that in spite of being a hypertensive patient, her blood pressure, monitored daily, stayed within the normal range of 130 mmHg/70 mmHg. Biochemical parameters, creatinine, liver function laboratory tests, TSH and EKG showed no changes with the combined treatment. Lithaemia was 0.66 mEq/L at the sixth week. No adverse effects were reported with the exception of dry mouth and moderate constipation, both well tolerated by the patient.

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Discussion

The combination of high doses of both clomipramine [Gervasoni *et al.* 2009] and mirtazapine achieved a high level of synergy, acting at pharmacodynamic level through triple serotonergic enhancement (reuptake inhibition by clomipramine, α -2 and 5-HT₂ antagonistic effects of mirtazapine) and dual noradrenergic enhancement (reuptake inhibition by clomipramine and its active metabolite desmethylclomipramine, antagonistic α -2 effect of mirtazapine). In addition, blockage of the 5-HT₂ and 5-HT₃ receptors achieved with mirtazapine can help to reduce the serotonergic sexual (5-HT₂) and digestive (5-HT₃) adverse effects of clomipramine. It is also known that sustained 5-HT₂ blockage improves sleep and increases the gene expression of the 5-HT_{1A} receptor (synergy between 5-HT₂ antagonism and 5-HT_{1A} stimulation) [Ruiz-Doblado *et al.* 2010]. In addition, both clomipramine and mirtazapine were considered two of the most effective antidepressant drugs in a recent review of the evidence [Montgomery *et al.* 2007]. Furthermore, lithium enhancement has a stabilizing effect on membranes and also on sodium cellular transportation, as well as the upregulation of gene expression associated with neurotransmission via second messengers (phosphatidylinositol). Finally, partial rapid eye movement sleep deprivation, during the second half of the night, can enhance pharmacological effect. Although its efficacy is known at the empirical level, the mechanism of action of its antidepressant effect remains unclear. Nowadays there are 'cleaner' combinations in treatment algorithms for resistant melancholia, such as those associating venlafaxine or duloxetine (both dual 5-HT-NA antidepressants) with a second antidepressant or mood regulator [Hannan *et al.* 2007; De la Gándara *et al.* 2008; Yazici, 2009], but some works have shown that the noradrenergic effect of these new drugs may be inferior to that of clomipramine, which achieves a powerful noradrenaline reuptake inhibition due to both the drug itself and its metabolite (clomipramine + desmethylclomipramine) [Gillman, 2007].

According to our current state of knowledge, this is the first documented case of response to this combination of drugs in resistant melancholia at these doses. The conclusions to be drawn, without losing sight of the limitations intrinsic to a case report, suggest the use of combination and energetic enhancement in the management of

resistant melancholic depression, given that, although they are not supported by the results of clinical trials, they are supported by their pharmacological rationality, their molecular synergy and their tolerability and efficacy in naturalistic, 'real clinical practice' conditions. Therefore, the use of the old tricyclics, which are powerful, widely documented and have proven efficacy in melancholia, should not be ruled out when designing combination strategies. This case does emphasize the need for additional studies with larger samples for documenting the efficiency of this and other combinations in resistant melancholic depression. This would give psychiatrists more aggressive, fast-acting combination strategies with a reasonable safety margin.

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Conflict of interest statement

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References

- Blier, P., Ward, H., Tremblay, P., Laberge, L., Hebert, C. and Bergeron, R. (2010) Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. *Am J Psychiatry* 167: 281–288.
- De la Gándara, J., Agüera, L., Ferre, F., Rojo, J. and Ros, S. for the Group for the Study of Antidepressants Associations (2008) Algorithm for the management of treatment-resistant depressions based on the antidepressants combination. *Eur Neuropsychopharmacol* 18(Suppl. 4): 328.
- Gervasoni, N., Aubry, J., Gex-Fabry, M., Berstch, B. and Bondolfi, G. (2009) Is there a place for

tricyclic antidepressants and subsequent augmentation strategies in obtaining remission for patients with treatment resistant depression? *Pharmacol Res* 59: 202–206.

Gillman, P. (2007) Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 151: 737–748.

Hannan, H., Hamzah, Z., Akinpeloye, H. and Meagher, D. (2007) Venlafaxine–mirtazapine combination in the treatment of persistent depressive illness. *J Psychopharmacol* 21: 161–164.

Montgomery, S., Baldwin, D., Blier, P., Fineberg, N., Kasper, S., Lader, M. *et al.* (2007)

Which antidepressants have demonstrated superior efficacy? A review of the evidence. *Int Clin Psychopharmacol* 22: 323–329.

Ruiz-Doblado, S., Rueda-Villar, T., Zurita-Gotor, P. and Sanz-Cortés, S. (2010) Venlafaxine plus mirtazapine as first-line treatment for melancholia: preliminary results. *J Psychopharmacol* 24: 1837.

Rush, A., Wardenm, D., Wisniewskim, S., Favam, M., Trivedim, S., Gaynesm, B. *et al.* (2009) STAR*D: Revising conventional wisdom. *CNS Drugs* 163: 1531–1541.

Yazici, O. (2009) After STAR*D: Treatment resistant depression. *Noropsikiyatri Arsivi* 46: 61–69.

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