# CALIFORNIA ROCKET FUEL – COMBINGING MEDICATION AGAINST DEPRESSION

Dr Christian Jonathan Haverkampf, M.D.

**The association of the SNRI venlafaxine (Effexor®) and the NaSSA mirtazapine (i.a. Remeron®), is in the literature often referred to as California Rocket Fuel (CRF). Some studies have shown advantages in terms of efficacy and rapid control of depressive symptoms compared to other combinations. However, at the same time the combination can also lead to an increase in side effects, which can be potentially quite serious. It is therefore important to be quite clear not only about the existing condition, but also to carefully evaluate the risk-benefit trade-off in the individual case, and discuss this with the patient.**

Keywords: California Rocket Fuel, CRF, SNRI, NaSSA, venlafaxine, duloxetine, mirtazapine, antidepressants, medication, treatment, psychiatry

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# Introduction

Treatment-resistant depression is very common, causing significant human suffering and economic loss to the whole of society. The combination of a specific serotonin and norepinephrine reuptake inhibitor (SNRI), such as venlafaxine (Effexor®), and the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine (i.a. Remeron®) is a quite frequently used option. The result is a potent noradrenergic and serotonergic effect. Unlike many other antidepressants, mirtazapine does not inhibit the reuptake of serotonin, norepinephrine, or dopamine, nor does it inhibit monoamine oxidase.

The first-line treatment for depression should usually embrace a combination of psychotherapy and medication (Haverkampf, 2018d), unless the depression is particularly mild, where psychotherapy by itself is often sufficient. However, one has to recognize that depression almost always has three causative factors the biological predisposition, the psychological dynamics and the environmental dynamics an individual is exposed to. The author has described a communication based approach to psychotherapy, Communication-Focused Therapy (CFT), elsewhere (Haverkampf, 2010, 2017b, 2017a, 2018c).

Once antidepressant monotherapy has been exhausted, often in the form of a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI), one needs to begin considering combinations. However, before switching to a combination, it is important that a sufficient dose has been tried, and usually a switch been made to another SSRI or to an SNRI, if the first medication is an SSRI, or to an SSRI if the first medication is an SNRI. A monotherapy may sometimes not be possible if time is of the essence.

The combination options may include two antidepressants with different mechanisms of action (e.g., bupropion + SSRI or mirtazapine + venlafaxine), adding other medications such as lithium or certain atypical antipsychotics (olanzapine, aripiprazole, or quetiapine) to the antidepressant, or even adding a

natural product. (Haverkampf, 2018b; Preston & Shelton, 2013) Psychotherapy should in the majority of cases be used, while several approaches, including psychodynamic psychotherapy, CBT, IPT and others have demonstrated their effectiveness. (Haverkampf, 2018d, 2018a)

Some studies have shown advantages in terms of efficacy and rapid control of depressive symptoms compared to other combinations. Due to mirtazapine's sedating and sleep inducing effect, it seems logical to add mirtazapine to antidepressants which are only partially effective, especially if the patient is experiencing insomnia. (Dunner, 2014) Duloxetine and mirtazapine may also elicit their therapeutic effect by modulating the activity of apoptotic and neurotrophic pathways, thus enhancing plasticity and cell survival in depressive patients, as structural alterations in the limbic system, neuronal cell loss, and low levels of neurotrophins have been implicated in the pathogenesis of depression. (Engel, Zomkowski, Lieberknecht, Rodrigues, & Gabilan, 2013)

## The Serotonin Transporter (SERT)

The current generation of antidepressant drugs acts predominantly by targeting the serotonin transporter (SERT). The original trend to do this selectively (e.g., with SSRIs or selective serotonin reuptake inhibitors) has given way to combining various additional pharmacologic mechanisms with SERT inhibition, including dual actions by single drugs (e.g., SNRIs or serotonin norepinephrine reuptake inhibitors), or by augmenting SSRIs with a second drug of a different mechanism (e.g., bupropion with dopamine and norepinephrine reuptake inhibition; trazodone with 5HT2A antagonism; mirtazapine with 5HT2A/5HT2C/5HT3/alpha2 antagonism; buspirone or some atypical antipsychotics with 5HT1A partial agonism; other atypical antipsychotics with 5HT2C/5HT7 antagonism and other mechanisms). (M. Stahl, Lee-Zimmerman, Cartwright, & Ann Morrissette, n.d.)

# SNRI: Venlafaxine and Duloxetine

Venlafaxine has demonstrated its efficacy as monotreatment in depression in several studies. It is also aside, and often after an SSRI has been tried, one of the first line medications for anxiety, although an

increase in anxiety may be notice in the beginning. In a post hoc pooled subgroup analysis of 1573 patients results supported the efficacy of venlafaxine extended release for major depressive disorder treatment in patients with anxiety symptoms. (Lyndon, Prieto, Wajsbrot, Allgulander, & Bandelow, 2019)

Data from studies suggests a marginally higher toxicity of venlafaxine in overdose compared with another SNRI duloxetine and the SSRIs, although this may be related to differential patterns of prescribing in high-risk patients. Based on a review by Taylor and colleagues SNRIs have a positive risk benefit profile in the treatment of depression and generalized anxiety disorder in primary care, especially as second-line agents to SSRIs. (Taylor, Lenox-Smith, & Bradley, 2013) Interestingly, in a comprehensive systematic review and meta-analysis of placebo-controlled, double-blind RCTs, which examined the efficacy of duloxetine and venlafaxine in the acute treatment of major depressive disorder comprising 71 studies, the placebo effect sizes, defined as pre-postscore change divided by baseline standard deviation, differed significantly between venlafaxine and duloxetine studies, suggesting that the investigated drug has an influence on the placebo response that is not related to baseline severity, changes over the years or other variables. (Breilmann, Furukawa, Becker, & Koesters, 2018)

Venlafaxine, possibly more so than duloxetine, seems to be an appropriate alternative to SSRIs, particularly if they are not tolerated or not effective. In a meta-analysis of randomised controlled trials identified through bibliographical databases and other sources, both duloxetine and venlafaxine showed superior efficacy (higher remission and response rates) and inferior tolerability (higher discontinuation rates due to adverse events) to placebo. Venlafaxine had superior efficacy in response rates but inferior tolerability to SSRIs, and no differences in efficacy and tolerability to tricyclic antidepressants. Duloxetine did not show any advantages over other antidepressants and was less well tolerated than SSRIs and venlafaxine (Schueler et al., 2011)

# Mirtazapine

Mirtazapine has antihistamine, α2-blocker, and antiserotonergic activity. It is specifically a potent antagonist or inverse agonist of the α2A-, α2B-, and α2C-adrenergic receptors, the serotonin 5-HT2A, 5-HT2C, and the histamine H1 receptor. It enhances, therefore, the release of norepinephrine and 5-HT1A-mediated serotonergic transmission, which is probably responsible for mirtazapine's rapid onset of action.

(Anttila & Leinonen, 2001) Its antagonist effect on the presynaptic receptors seems to reduce the latency of the antidepressant response. Moreover, its robust noradrenergic effect enhances the serotoninergic effects of the most common antidepressants. (Álvarez & Viñas, 2010) As an H1 receptor antagonist, mirtazapine has probably the greatest potency among all antidepressant groups. At low dose it turns into a selective H1 receptor antagonist. Since mirtazapine has weak or no activity as an anticholinergic or blocker of sodium or calcium channels, in contrast to most tricyclic antidepressants, it appears to have better tolerability and low toxicity in overdose.

Increases in appetite and body weight as well as dry mouth and sedation are the most common adverse effects. Although, in clinical practice the daytime sedation often attenuates or disappears within a week or less. In contrast to selective serotonin reuptake inhibitors (SSRIs), mirtazapine has no sexual side effects and can even ameliorate the side effects of other antidepressants. In major depression, its efficacy has been shown to be comparable to that of amitriptyline, clomipramine, doxepin, fluoxetine, paroxetine, citalopram, or venlafaxine.. (Anttila & Leinonen, 2001)

The findings of an analysis of a therapeutic drug monitoring database containing plasma concentrations of venlafaxine and its active metabolite O-desmethylvenlafaxine with 1067 patients suggested an inhibitory effect of doxepin on venlafaxine metabolism, but mirtazapine was less likely to lead to venlafaxine metabolism alterations. (Paulzen et al., 2018)

# Venlafaxine and Mirtazapine (California Rocket Fuel)

Adding mirtazapine to venlafaxine was shown to be relatively safe in the STAR*D study. (Dunner, 2014) In one study the combination of mirtazapine and venlafaxine was administered to 32 patients with persistent depressive illness and a mean of 2.5 previous antidepressant trials. Clinical response rates were 44% at 4 weeks and 50% at 8 weeks. At 6-month review, 18 patients (56% of the original cohort and 75% of those still receiving treatment) had significantly responded. Among the adverse effects sedation (19%) and weight gain (19%) were the most frequent ones. (Hannan, Hamzah, Akinpeloye, & Meagher, 2007) In another study with a prospective case series twenty-two depressed patients with major depression were treated with venlafaxine and mirtazapine in combination for an average of just under 8weeks. At baseline, mean psychometric depression scores reflected a cohort at the moderate to severe end of the spectrum.

Mean duration of treatment was approximately eight weeks, producing a response rate of 81.8% and a remission rate of 27.3%. However, nearly half had significant side-effects during treatment. (Malhi, Ng, & Berk, 2008)

# Hypomanic Switching

There is a risk that using a potent combination such as CRF can lead more easily to switching into hypomanic or even manic states than using solely an SSRI. Meagher and colleagues describe two cases that highlight the potential usefulness of duloxetine used in combination with mirtazapine that also emphasise the danger of drug-induced hypomanic switching. (Meagher, Hannan, & Leonard, 2006) The authors describe two cases that highlight the potential usefulness of duloxetine used in combination with mirtazapine that also emphasise the danger of drug-induced hypomanic switching. (Meagher et al., 2006) Mustafa and colleagues report a case of a 41 year old woman with recurrent depression and with no previous history of mania or hypomania, who developed severe mania and required management in a Psychiatric Intensive Care Unit after receiving duloxetine at 30 mg per day which is only half the recommended starting dose. (Mustafa, Almoshmosh, Al-Robb, & Abukmeil, n.d.) On the other hand, Lai and colleagues present a case of treatment-resistant depression with full recovery where a combination of mirtazapine and bupropion was used after a failed response to combined mirtazapine and duloxetine treatment. (Lai, 2009)

# Serotonin Syndrome

All drugs that directly or indirectly increase central serotonin neurotransmission at postsynaptic 5-HT1A and 5-HT2A receptors can produce the potentially lethal, but otherwise rare serotonin syndrome, and every clinician who uses serotonergic medication should be familiar with the symptoms and the needed interventions. Individual vulnerability appears to play a role in its development. A combination of two serotonergic drugs, such as venlafaxine and mirtazapine, can have a higher chance of triggering it. Houlihan reported a serotonin syndrome resulting from the addition of tramadol to a medication regimen of venlafaxine and mirtazapine. The author suggests that it was likely that the activation of 5-HT1A

receptors by mirtazapine, the combined serotonin reuptake inhibition by venlafaxine and tramadol, as well as possible serotonin release by tramadol, contributed to the development of the serotonin syndrome in this case. (Houlihan, 2004)

# Conclusion

Patients with insomnia and weight loss may benefit from California Rocket Fuel. It has been used more often recently as a first-line choice, particularly in cases where there is also insomnia, and maybe also anxiety. Despite its use in most studies for cases of drug-resistant depression, there are newer studies that recommend CRF as a first line option. (Silva, Mota, & Azevedo, 2016) Using also the illustration of a case study where an improvement was noticed after two weeks of treatment and the stabilization of depressive symptoms were achieved by the fourth month, the authors conclude that CRF seems to be effective and useful.

Quite often, what leads to the use of the combination may actually be a treatment with a monotherapy of either antidepressant at the outset where the other antidepressant is later added on. For example, if sleep difficulties surface or continue on venlafaxine, one may often think of adding on mirtazapine, or, if mirtazapine does not lead to a satisfactory reduction in depressive symptoms and causes too much weight gain, adding on mirtazapine could appear to be a sensible choice. However, it needs to be remembered that the empirical evidence for its superior efficacy as compared to a monotherapy is still tenuous. Also, there is a higher risk of side effects, and some of them, even if rare, can be quite serious.

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*Dr Jonathan Haverkampf, M.D. (Vienna) MLA (Harvard) LL.M. (ULaw) BA (Dartmouth) trained in medicine, psychiatry and psychotherapy and works in private practice for psychotherapy, counselling and psychiatric medication in Dublin, Ireland. The author can be reached by email at jonathanhaverkampf@gmail.com or on the websites www.jonathanhaverkampf.com and www.jonathanhaverkampf.ie.*

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