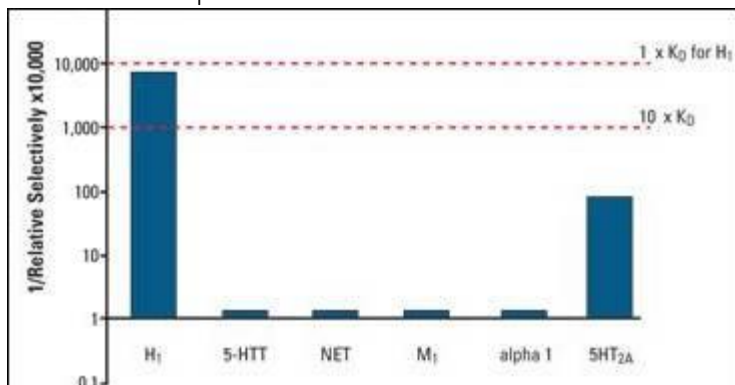




TODAY'S TOPIC: Mirtazapine and Weight Gain: Truth or False?

Background:

Mirtazapine, an atypical antidepressant, was first synthesized in the Netherlands in 1987 and was introduced in the United States in 1996. It is a potent serotonin 5-HT₂ and 5-HT₃ and alpha-2 antagonist, thereby increasing serotonergic stimulation via the 5-HT₁ receptor, and has a low affinity for muscarinic, cholinergic receptors. It has no significant affinity for dopamine receptors, and no effect on monoamine reuptake.



Trials of mirtazapine in the treatment of weight loss were motivated by weight gain being one of the most common side effects. At that time, it was attributed to increased appetite and food cravings (especially carbohydrates). Although the exact mechanism is not known, some suggest mirtazapine-induced weight gain may be secondary to its effects on 5-HT_{2c} and H₁ receptors.

Importance:

Palliative care providers often prescribe mirtazapine for appetite stimulation. Weight loss and fatigue (from a lower intake of calories) is common in older adults and those with serious illness. Palliative care providers should be aware of, and thoughtful of reasonable expectations for, this potential correlation.

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The Literature:

- [CNS Drug Rev. 2001 Fall;7\(3\):249-64.](#)

A review of the pharmacological and clinical profile of mirtazapine.

- Safety: "The incidence of the most common side effects of mirtazapine was reviewed in a meta-analysis by Fawcett and Barkin" [Ref]

	Mirtazapine	Placebo
Overall incidence rate of adverse clinical experiences	65	76
Nervous system (central, peripheral and autonomic)		
Drowsiness	23.4*	14.2
Excessive sedation	18.7	5.2
Insomnia	9.5	7.3
Agitation	8.6	7.3
Restlessness	5.0	7.3
Headache	5.4	10.4**
Vertigo	6.1	4.3
Appetite decreased	12.8	12.2
Appetite increased	10.6*	2.1
Gastrointestinal and metabolic/nutritional		
Dry mouth	25.3*	15.9
Constipation	13.1	11.9
Body weight decrease	1.9	6.1**
Body weight increase	10.3*	1.2
Others		
Fatigue	16.2	11.9

* $p < 0.05$ vs. placebo. ** $p < 0.05$ vs. mirtazapine.

- *Discussion:* note the differences in weight decreased and increased

- [J Clin Psychiatry. 2001 Oct;62\(10\):782-8.](#)

Efficacy of mirtazapine for prevention of depressive relapse: a placebo-controlled double-blind trial of recently remitted high-risk patients.

- Method: An intent-to-treat sample of 410 patients meeting DSM-IV criteria for moderate-to-severe recurrent or chronic major depressive episodes began 8 to 12 weeks of open-label therapy with mirtazapine (flexibly titrated, 15-45 mg/day)
- Results: Mirtazapine therapy reduced the rate of depressive relapse by more than half, with 43.8% of patients relapsing on treatment with placebo as compared with 19.7% of the mirtazapine-treated patients.
 - Although weight gain was significantly greater in the group receiving active medication during the double-blind phase ($p = .001$), patients taking mirtazapine gained only 1.4 kg (3.1 lb) across the 40 weeks of continuation therapy, and there was no difference in the rates of weight gain as a new onset adverse event.
- Conclusion: "Continuation-phase therapy with mirtazapine is effective and well tolerated."
- *Discussion:* Of note, this was self-reported weight gain. To add, specifically this study found weight gain during the 40 weeks of the continuation phase was only about half the weight gain observed during the first 8 to 12 weeks of therapy.

So... What does this all mean Jenn?

- Mirtazapine does appear to have a statistical significant difference in weight gain
- However, whether this is a clinical significant difference is up to you. On average patients may gain about 3 lbs and this occurs usually within the first 8 to 12 weeks
- Is there a dose dependent effect? I am sure all of you have heard that mirtazapine at lower doses targets more of sleep and appetite, and over 30mg/day you are utilize mirtazapine for depression and anxiety.... Well this is half-true:
 - There are pharmacokinetic studies that suggest mirtazapine's affinities change with dose changes: [\[Ref\]](#). It is not so much that there is less of an alpha-1 or H1 reduction but more of a NE increase with dosing increases... so more stimulation can appear to be less sedating
 - However, this has never been shown in clinical studies - see above where patients could receive up to 45mg/day
- So? I would consider mirtazapine for weight gain – but be reasonable with patients and yourself. This medications may only improve weight by patient reported gains of about 3 lbs and it appears to happen fast. If patients have been on this medications for a long time, with minimal improvements (here comes my favorite word..): deprescribe!

Geriatric Considerations:

- Mirtazapine is often considered a geriatric friendly antidepressant. It is usually well tolerated in older adults. The most common adverse drug reactions are dry mouth and drowsiness

Stay tuned for future PCP Phast Phacts on mirtazapine!

CLINICAL PEARL:

Literature suggests mirtazapine can increase patient's weight by 3 lbs within the first 8-12 weeks of therapy.