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The Gravity of Weight

Down the Rabbit Hole: When Medication Leads to Weight Gain

A particularly vicious circle when prescription medication makes you fat

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Many medications, including antidepressants, antipsychotics, mood stabilizers, corticosteroids, beta-blockers, hormonal contraceptives, insulin, and even medications for allergy such as diphenhydramine (Benadryl), cause weight gain--even considerable weight gain--in susceptible patients. Far more medications result in weight gain than in weight loss. Initially there were only anecdotal reports of weight gain with prescription medications but the extent of the problem was delineated

Many common medications lead to weight gain

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when Allison and his colleagues conducted comprehensive literature searches (Cheskin et al, 1999; Allison et al, 1999) almost 15 years ago and found medication-related weight gain was “under-recognized” by clinicians and sometimes resulted in patients’ noncompliance with treatment.

How much weight is someone willing to gain when he or she is on a medication? That question was posed by Sansone and colleagues about ten years to a sample population of over 200 Midwestern, suburban (and primarily women) in a primary care practice. For either a medical or psychiatric non-life threatening condition, this sample would accept a weight gain of about 5 1/2 pounds. If the medical or psychiatric condition involved a life-threatening condition, people were able to tolerate a weight gain of 13 pounds or higher. Of note, though, in this particular sample, more than 5% were unwilling to gain any weight. In other words, for some, any weight gain is intolerable, regardless of the efficacy of the medication prescribed. For others, though, it is not just an issue of aesthetics: weight gain produced by medication may

lead to serious metabolic abnormalities such as insulin resistance, hypertension, abnormal blood lipid levels, and even overt type 2 diabetes in those genetically vulnerable. This is particularly common in the so-called second generation antipsychotics.

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Medications can cause weight gain in the short term (within the first 8 to 12 weeks) and the long term (several months to a year), according to Hasnain and Vieweg, in the journal *Postgraduate Medicine* (2013.) There is a suggestion that those who gain weight in the first several weeks of treatment are more likely to continue to gain, though some medications like the selective serotonin reuptake inhibitors (SSRIs) result in some weight loss initially but ultimately weight gain over the year.

Why do some medications cause weight gain? There are several factors, and the more mechanisms involved, the more likely weight gain will occur. For example, some medications may cause an increase in appetite specifically by receptor blockade. Wysokiński and Kloszewska in a recent article in the *Journal of Advanced Clinical Pharmacology* (2014) reviewed the complex hormonal system involved in short-term satiety and long-term energy storage. These authors note that histamine H1 blockade and serotonin 5-HT2C receptor antagonism are responsible for the weight gain that is seen with antipsychotics such as clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), and risperidone (Risperdal), as well as antidepressants such as some of the SSRIs, most notably with paroxetine (Paxil). Because a medication such as aripiprazole (Abilify), used primarily to treat psychosis but also now marketed (and highly advertised on TV) as an adjunct for treatment of depression, is a partial agonist, rather than an antagonist, it is generally thought of as weight neutral and may sometimes be substituted for those that cause the most weight gain such as clozapine and olanzapine. H1 receptor blockade is also responsible for weight gain with antidepressants, such as mirtazapine (Remeron) and trazodone (Desyrel), or the antihistamine such as hydroxamine (Vistaril.)

Other medications increase appetite by a direct effect on the many hormones involved in appetite regulation, including leptin, ghrelin, and insulin. For example, some antipsychotics (e.g. clozapine and olanzepine) also block the action of leptin, resulting in increased, but ineffective levels of this hormone (leptin resistance) and accumulation of fat tissue. Both antipsychotics and antidepressants can also affect the levels of insulin, creating a state of insulin resistance and even an increased risk of type 2 diabetes. Wysokiński and Kloszewska caution, however, that changes in these hormones may be secondary to weight gain rather than the cause of weight gain.

Sometimes, medications don't affect appetite but rather can change (i.e. decrease) a person's resting metabolic rate and hence cause weight gain. This has been seen with the older tricyclic antidepressants such as impramine (Tofranil). Further, tumor necrosis factor alpha (TNF-α) is a cytokine that can also lead to weight gain with some of the antipsychotics such as clozapine and olanzapine, but also with lithium, amitriptyline (Elavil), and mirtazapine. Wysokiński and Kloszewska report that activation of this TNF-α system seems to occur early in treatment and might eventually become a sensitive marker that weight gain will occur. Other mechanisms resulting in weight gain include drinking highly caloric beverages because of dry mouth that may accompany medication or even increased sleeping time due to the sedating effects of medication and hence less energy expenditure. Sometimes patients are taking several medications at once, and concomitant medications may interact in a way to increase weight gain. Further, ethnicity, gender, and age also contribute to differences in medications' effects on weight. For example, some studies report that weight gain is more common in women and more likely to occur in those predisposed to excessive weight in general.

Many of these mechanisms involve mutations in specific genes and eventually genomic studies will lead to more specific individual recommendations for patients. For example, some patients are "poor metabolizers" and some are "ultra-rapid metabolizers," according to Altar et al, writing in the *International Review of Psychiatry* (2013.)

Bottom line: Weight gain can occur in both the short and long term and may interfere with treatment compliance. Clinicians should monitor patients carefully for weight-related and metabolic changes, as well as educate patients regarding healthy lifestyle choices of diet and exercise. It is often possible to switch to a more weight neutral medication or be able to lower the dose of the offending medication. Eventually, there will be more widely available genetic screenings that will lead to individualized recommendations.

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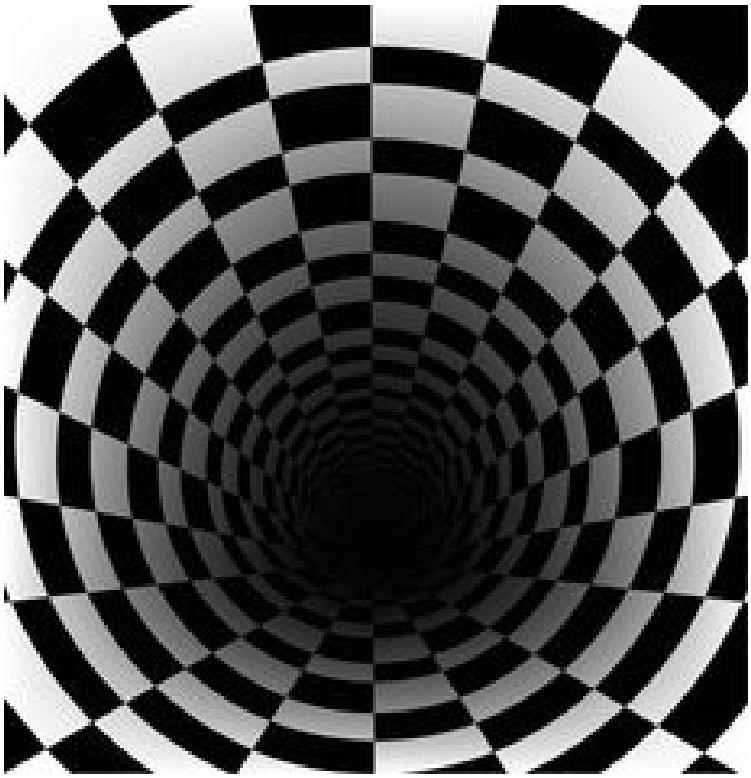

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About the Author

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In Print: *The Gravity of Weight: A Clinical Guide to Weight Loss and Maintenance*

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