See article by Vandenberghe et al

Psychotropic Agents and the Prediction of Weight Gain

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Weight gain is a common side effect among psychotropic agents, including antipsychotics, mood stabilizers, and some antidepressants. The ability to predict both treatment response and adverse events on individual patients is a goal not yet available with the use of psychotropic agents. Hopefully when psychopharmacologic treatments become tailored therapies, we will reach such a gold standard. For now, an alternative would be the identification of predictors based on group demographic characteristics or clinical variables. In this issue of the *Journal*, Vandenberghe and colleagues[1] present data using this approach. The authors report an observational study of 351 patients who were prospectively followed for 1 year at the Lausanne University Hospital in Switzerland. Their main goal was to determine the predictive power of an early (1-month) weight gain on longer term (1-year) weight gain, following the initiation of a psychotropic agent known to produce this effect.

The authors found that a weight gain of > 5% after 1 month was the best predictor for weight gain 1 year later. Their analysis identified most patients who had weight gain after 1 month as continuing to have a moderate weight gain after 3 and 12 months. Also of note, increase of physical activity and appetite in the first 30 days of treatment did not have predictive power for weight gain.

Vandenberghe and colleagues' findings[1] validate The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes guideline.[2] The guideline recommends that weight gain of > 5% associated with pharmacologic treatment should lead the prescriber to reconsider the continuation of a given treatment.[2] The added value of the authors' report is the discovery of a specific point of time that appears to be best to first consider change in pharmacologic treatment.

This report highlights the importance of extended planning in the care of the severely mentally ill who, in most cases, require long-term treatment with pharmacologic agents. Good clinical practice, in part, should be based on our ability to predict, in a timely manner, long-term side effects caused by weight gain. These include hypertension and metabolic syndrome that eventually lead to decreased life expectancy of more than 2 decades compared to the general population.[3] Risks and benefits need to be balanced early. Unfortunately, some risks, such as weight gain with antipsychotic agents, which is known to be high in the early stages of treatment, may not "plateau" but may remain ongoing.[4] Clinicians should also keep in mind that weight gain is multifactorial; lifestyle changes in diet and exercise are essential in the management of patients taking weight-gaining psychotropic agents.

This report, however, has a number of limitations, most of which are recognized by the authors. For example, due to the relatively small sample size, the data could not be stratified by specific treatments. Also, differences regarding duration of previous exposure to psychotropic agents were not controlled, with the consequent heterogeneity of the sample in regard to previous exposure. Stratification by patients naive to psychotropic treatment and different duration of exposure is not possible. Another concern is that the majority of patients (55%) were lost to follow-up, so biased results in either direction cannot be ruled out. An additional factor is common to all observational studies: the generalizability of the findings to other patient populations may also be limited. Although the current study was conducted under what appears to be standard clinical conditions in a Swiss university hospital, the data may not be generalized to clinical samples in the United States or other parts of the world where demographics and lifestyles of the study populations are different. Prescribing practices, including drug preferences and combinations, may also vary. Also, the prevalence of obesity of 17% at baseline for this European population is smaller than the average of 55% in patients with severe mental disorders found worldwide.[5]

More studies are needed, especially of longer duration. In addition, course of weight gain is not the same for all pharmaceuticals; therefore, we need large sample sizes in order to stratify by treatment to learn more about each individual drug. Furthermore, since most of our patients are treated with more than 1 drug, we need to learn more about additive or even synergistic weight gain interaction across different agents. As the authors note, previous reports on the same topic have been conducted with secondary analyses of clinical trials with specific treatments,[6–8] which would complement the current study findings. In addition to weight gain, we need to focus on the increase of abdominal circumference, which is known to be correlated with poor health.[9] Also, the long-term value of exercise and diet to prevent weight gain caused by psychotropic agents is still not clearly understood. Other variables such as ethnicity and age need to be considered. We need to learn more about how weight gain affects the course of illness across different disorders.[10,11] Given that early increase of triglyceride levels,

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with or without weight gain, has been correlated to long-term risk of diabetes, we need to better understand the interaction between weight gain and change in blood lipids.[6] The correlation between increased appetite and weight gain is also not always present[8]; hence, we need to better understand its significance as well. Furthermore, concerns about the consequences of weight gain in individuals with mental disorders should start very early after the initiation of treatment, as its effects may be long term.[12] Finally, studies to better understand individual predisposition to weight gain by determining genetic factors that identify patients at risk of antipsychotic-induced weight gain need to continue and, ideally, incorporate this knowledge into clinical practice.[13]

To summarize, regardless of the limitations with the Vandenberghe et al study,[1] this author finds the article's take-home message in patients' best interest. Under standard clinical conditions, any time a new psychotropic agent is introduced to a patient, a weight gain of more than 5% during the first month after its initiation should result in thoughtful review of risks and benefits because further weight gain and other clinically meaningful adverse events can be expected. Clinicians should have this important discussion with their patients and, together, determine the course to take.

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