Weight gain risk factor assessment checklist: overview and recommendation for use

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Abstract

OBJECTIVES: Patients with mental illness are at risk for weight gain. Evidence-based risk assessment checklists have the potential to identify patients at risk early in treatment and improve patient outcomes.
METHODS: The 16-item Weight Gain Risk Factor (WGRF-16) checklist has been developed as a simple brief assessment of key weight gain risk factors during antipsychotic treatment. It consists of factors that were collected on the basis of published research on predictors to be assessed at initiation of, and early in treatment with antipsychotics.
RESULTS: The factors in the WGRF-16 checklist included age, sex, body mass index, race, appetite, energy intake, a diagnosis of undifferentiated schizophrenia, early clinical response, comorbiditites, social activity, patient insight, housing conditions, weight satisfaction, eating habits, and physical activity level. The WGRF-16 is designed to be repeated 2–3 weeks after initiation of treatment to help to predict an individual's risk of clinically significant weight gain (>7%) during long-term treatment. Further research is required to assess the predictive validity of the checklist.
CONCLUSIONS: The WGRF-16 checklist is not intended to replace other required monitoring of patients with severe mental disorders but is a facilitator of weight monitoring in conjunction with clinical guidelines.

ORIGINAL ARTICLE

INTRODUCTION

Patients with schizophrenia have elevated standardized mortality ratios in comparison with the general population (Saha *et al.* 2007). Mortality in these patients is greater than would be predicted from the incidence of medical conditions, suggesting either deficiencies in monitoring, diagnosis or clinical care (Kisely *et al.* 2009). Although certain risk factors may be modifiable with lifestyle and weight control programs, more effort is needed to identify patients at risk and increase the awareness and educate early in their treatment. The analysis of a multinational study confirmed that if physicians implement lifestyle changes with educational programs around onset or prior to treatment initiation, then the probability of gaining weight is lower in the long term versus initiating programs later in the course of treatment where body mass index (BMI) is already elevated (Pendlebury *et al.* 2007; Kahn *et al.* 2008; Treuer *et al.* 2009; Solutions for Wellness 2010).

Although checklists have tremendous potential to improve safety and quality and reduce costs of health care, they are underused (Winters *et al.* 2009). Screening checklists can improve patient outcomes by assessing risks, sharing knowledge and helping ensure that all patients receive evidence-based clinical care and monitoring. It is clear that a checklist can help clinicians identify at-risk patients early in treatment, and that early management of risk factors for weight gain can result in improved patient outcomes (Pendlebury *et al.* 2007; Poulin *et al.* 2007; Bushe *et al.* 2008; Holt *et al.* 2010; Porsdal *et al.* 2010). To this end, we have completed a literature search to identify and summarize risk factors for weight in patients with severe mental illness. Our aim to provide a simple checklist that clinicians can use in everyday practice led to the development of the WGRF-16 Checklist – the Weight Gain Risk Factor prediction tool.

Individuals with schizophrenia have significantly higher mortality rates compared to the general population that are only recently showing some evidence of decline (Tiihonen *et al.* 2009; Bushe *et al.* 2010). Patients with schizophrenia have elevated standardized mortality ratios for almost all types of illness in comparison with the general population (Saha *et al.* 2007). Of specific concern is that mortality is greater than would be predicted from the incidence of medical conditions, suggesting either deficiencies in monitoring, diagnosis or clinical care (Kisely *et al.* 2009). There is also evidence to suggest that much of this mortality is avoidable (Crompton *et al.* 2010).

Severe mental illness itself, defined here as schizophrenia or bipolar disorder, together with the well-known risk factors may represent the main drivers for the increased risk of physical illness and weight gain in these patients. However, many patients are already overweight when treatment-naïve (Kahn *et al.* 2008; Perez-Iglesias *et al.* 2008). The potential role of antipsychotic and other psychotropic medications may also be important (Remington 2006; Saha *et al.* 2007). Although certain risk factors may be modifiable with lifestyle and weight control programs, more effort is needed to increase the awareness and education about the predictive value of such factors, regardless of their treatment. In particular, patients in their first episode of psychosis are at the highest risk of adverse metabolic changes. The EUFEST study reported that at the end of the first year of treatment with antipsychotics approximately 50% of the patients had a BMI >25 kg/m^2 regardless of medication type (Kahn *et al.* 2008).

Lifelong treatment with antipsychotic medications is unavoidable in most cases, further complicating the potential for significant weight gain and obesity. Recent data suggests that there is a potential for significant longer-term weight gain (Millen *et al.* 2010). The wide adoption of second-generation antipsychotic drugs was believed to have the potential to increase mortality of patients with schizophrenia through worsening of metabolic parameters. However, a recent analysis of robust datasets reports that long-term treatment with antipsychotic drugs is associated with lower overall mortality compared with no antipsychotic use and this is most marked in first episode patients (Tiihonen *et al.* 2009). Other data is also suggestive that cardiovascular mortality and morbidity is in fact greater with the first generation antipsychotics (Osborn *et al.* 2007; Dean and Thuras 2009; Tiihonen *et al.* 2009; Bushe *et al.* 2010). Nevertheless, the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) is one of the largest randomized studies of patients with schizophrenia conducted to date with substantial statistical power (Strom *et al.* 2008), and this study did not detect an increased risk of non-suicide death associated with the use of ziprasidone vs. olanzapine. These results imply that excess mortality is rather related to illness factors and not necessarily related to cardiac issues. The risk of all-cause mortality or cardiovascular mortality was similar among ziprasidone and olanzapine users whereas the incidence of all cause hospitalizations was higher among those randomized to ziprasidone (Strom *et al.* 2010).

The recognition that schizophrenia is associated with metabolic comorbidity and a subsequent greater risk of cardiovascular events compared to the general population has led to attempts to reduce this metabolic burden (Bushe *et al.* 2005). Increased weight and smoking rates combined with less exercise and poor dietary choices have led to a variety of behavioural programmes and pharmacological agents being evaluated with the aim of improving lifestyle and managing weight (Bushe and Paton 2005). Long-term weight management of obese and overweight patients with severe forms of mental illness may be possible through the provision of simple lifestyle advice within a group or individual setting including acutely psychotic patients (Pendlebury *et al.* 2007; Bushe *et al.* 2008; Holt *et al.* 2010). In a case of

an individual patient experiencing weight gain, switching to another antipsychotic in an otherwise stable condition is not always an option because of the risk of relapse and due to a lack of alternative medication with a more suitable efficacy and tolerability profile (Treuer *et al.* 2009). Several reports demonstrate the potential effectiveness of a behavioural weight control programme including physical exercise in the prevention of weight gain during antipsychotic therapy and associated comorbid conditions in outpatients with schizophrenia and mood disorders (Poulin *et al.* 2007; Porsdal *et al.* 2010). Patients in their first psychotic episode are at a high risk for metabolic changes (Kahn *et al.* 2008) and recent data also shows that treatment naive patients do less physical activity (Spelman *et al.* 2007; Koivukangas *et al.* 2010).

There are several clinical baseline predictors for weight gain when starting treatment: younger age, male gender, a lower baseline body mass index, non-Caucasian race, increased appetite, increased energy intake, a diagnosis of undifferentiated schizophrenia and an improved clinical response [see summary in Treuer *et al.* 2008; 2009). Treuer and colleagues have reported significant additional predictive factors that have not previously been noted: comorbiditites, social activity, patient insight, housing conditions, weight satisfaction, eating habits and physical activity level (Treuer *et al.* 2009). Appetite change should also be considered in patient care, but when regular weight monitoring is performed, appetite may not contribute additional information predicting future weight changes during treatment with olanzapine; early weight change may be a more useful predictor for long-term weight change (Case *et al.* 2010).

Results of pooled trial databases provide additional information for clinicians to evaluate risk of substantial weight change or BMI increase for individual patients, based on data from 4 pooled studies in patients with bipolar disorder and based on the entire Lilly olanzapine database (Lipkovich *et al.* 2008; 2009). Weight gain of at least 2.0 kg at 3 weeks after initiation of olanzapine is a robust predictor of substantial weight gain, using various definitions of substantial weight gain. For instance, negative predictive values based on data from 2 schizophrenia trials suggest that approximately 87–88% of patients who gain less than 2 kg by week 3 will gain less than 10 kg after 26–34 weeks of olanzapine treatment (Lipkovich *et al.* 2008). In other words, if they do not experience early weight gain at week 3, then the probability of substantial weight gain with longer-term treatment is about 12–13%.

Factors predicting weight gain can be assessed in usual clinical settings, and a checklist facilitates data collection. Our aim is to provide a simple checklist that clinicians can use in everyday practice led to the development of the WGRF-16 Checklist – the Weight Gain Risk Factor prediction tool.

DESCRIPTION OF THE WGRF-16 CHECKLIST - WEIGHT GAIN RISK FACTORS -16

Suggested Usage

The WGRF-16 could be used at treatment initiation and then subsequently after 2–3 weeks of treatment to determine any early risk of weight gain. Data is supportive of 2–3 weeks as an appropriate time to make an initial assessment of potential longer-term weight gain. The tool, however, can be used at any time and there may be benefit to its usage on a regular basis including when changes in medication and dose changes are made.

Components

The following 16 factors of the WGRF-16 were derived from published research literature and clinical data reports (Appendix 1): younger age, male gender, low baseline body mass index, non-caucasian race, increased appetite, high energy intake, diagnosis of undifferentiated schizophrenia, other medical comorbiditites, low social activity, poor patient insight, supervised housing conditions, eating until feeling full, poor eating habits, and low physical activity level. The following factors are assessed after the initiation of treatment: improved clinical response at week 3, increased weight gain (≥2 kg) at week 3.

The relevance of these factors and the scientific evidence are briefly summarized. A number of factors have been found to be consistently associated with weight gain during olanzapine therapy in patients with schizophrenia or bipolar disorder in studies over the last 10 years from a variety of research types. These include randomized controlled trials: younger age (Basson *et al.* 2001; Lipkovich *et al.* 2006; Strassnig *et al.* 2007; Smith *et al.* 2008); male gender (Lipkovich *et al.* 2006); a lower baseline body mass index (BMI) (Basson *et al.* 2001; Kinon *et al.* 2001; Kinon *et al.* 2005; Lipkovich *et al.* 2006; Saddichha *et al.* 2007; Ujike *et al.* 2008); non-Caucasian race (Basson *et al.* 2001; Lipkovich *et al.* 2006; Ujike *et al.* 2008); increased appetite (Basson *et al.* 2001; Kinon *et al.* 2005; Ujike *et al.* 2008); increased energy intake (Gothelf *et al.* 2002), a diagnosis of undifferentiated schizophrenia (Saddiccha *et al.* 2007), and an improved clinical response (Basson *et al.* 2001; Zipursky *et al.* 2005; Ujike *et al.* 2008). In addition, post hoc statistical analyses of data from several large randomized clinical trials demonstrated that a faster rate of weight gain during the early stages of olanzapine therapy (≥2 kg within the first 3 weeks) may be predictive of a greater amount of weight gain during continued olanzapine therapy (Kinon *et al.* 2005; Lipkovich *et al.* 2006, 2008, 2009). Although most of the research data on predictors for antipsychotic treatment emergent weight gain are derived from analyses of studies with olanzapine, recent trials indicate that these factors are predictive of weight gain during treatment with other

antipsychotics too, such as lower BMI at baseline and a diagnosis of undifferentiated schizophrenia (Saddiccha *et al.* 2007); and gender and younger age (Gebhardt *et al.* 2009).

Recent data also reported from a 6-month observational study evaluating specific clinical, eating- and lifestyle-related factors are associated with weight gain in patients initiating or switching to oral olanzapine for the treatment of schizophrenia or bipolar mania. This study enrolled 622 outpatients from four countries (China, Mexico, Romania and Taiwan; Treuer *et al.* 2009). Factors associated with weight gain with antipsychotic therapy included the following: Country and housing conditions, with less gain for patients living independently than in conditions where meals were provided for them – in hospital, supervised or family settings; Stronger appetite than usual; Eating until uncomfortably full; Meal frequency, ie. more than 3 times a day; Evening snack consumption; Thoughts preoccupied with food; Less than 30 minutes exercise per week.

Based on these data an evidence-based checklist was derived that could be used in clinical practice as an aid to provision of weight and lifestyle advice, programmes and education. Some of the factors proposed for inclusion into the checklist are continuous variables - younger age – where we were not able to propose a cut-off in an evidence-based manner lacking an exact threshold for this from research. However, this awareness could help clinicians evaluate them in a simple checklist based on their comparison with other patients. For "lower BMI" baseline BMI cut-off we propose about $<27\,kg/m^2$ (Lipkovich *et al.* 2006). For the actual checklist, we propose the following factors to consider at initiation of treatment: Younger age, Male gender, Low baseline body mass index, Non-Caucasian race, Increased appetite, High energy intake, Diagnosis of undifferentiated schizophrenia, Other medical comorbiditites, Low social activity, Poor patient insight, Supervised housing conditions, Eat until feeling full, Poor eating habits, Low physical activity level. In addition to these, we also propose to check the following factors at 3 weeks after initiation of treatment: Improved clinical response at week 3, Increased weight gain with ≥ 2 kg at week 3. The proposed checklist of the WGRF-16 can be found at the end of this paper in Appendix 1.

It is our intention that the WGRF-16 checklist be used for educational and awareness purposes. It should be used for patient screening as part of robust clinical care in conjunction with metabolic and weight monitoring advised in relevant guidelines (Saravene *et al.* 2009). Although not the function of the checklist, other monitoring is essential. The European Regulatory Agency has recently advised that patients treated with any antipsychotic agents should be observed for signs and symptoms of hyperglycaemia and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control and increased weight gain (European Medicines Agency 2010). Further clinical studies are required to assess the predictive validity of the WGRF-16 checklist in a naturalistic setting and ease of incorporation into clinical practice. Prospective studies can confirm the clinical benefits associated with its regular usage.

RECOMMENDATION AND STRATEGIES FOR CLINICAL USE

It is well established that weight gain is very commonly observed during therapy with antipsychotics (Taylor and McAskill 2000; Allison and Casey 2001; McIntyre *et al.* 2003). This WGRF-16 checklist may serve to help with routine physical health monitoring and is designed to compliment and not replace the required monitoring of patients with severe mental disorders according to the drug labeling and other appropriate guidelines. Any positive responses could indicate that the patient is in a higher risk category for significant weight gain during treatment, and physicians may consider assigning this patient to an appropriate weight control or lifestyle consultancy program, such as Solutions for Wellness (Solutions for Wellness 2010). It is to be expected that the majority of patients will fall into this category and require such management, either to reduce weight or prevent weight gain. Data is also suggestive that acutely psychotic patients may benefit from inclusion into these programmes albeit in a modified manner (Bushe *et al.* 2007). There are many types of programmes and individual availability will vary worldwide. This range from a telephone call centre to a 1:1 nursing program and each patient may require individual consideration as to the most relevant intervention (Hoffmann *et al.* 2005, 2008; Smith *et al.* 2008). The diagnosis of severe mental illness itself is a predisposing factor for weight gain, and these patients are likely to have other co-morbid physical illness due to modifiable risk factors and lifestyle, so there is no specific limit on the types or even numbers of programmes that may be utilised. For example, rehabilitation programs, weight education or any other psychoeducational programmes could be offered to these patients regardless of treatment and regardless of WGRF-16 results. For each antipsychotic, the relevant licenses will give clear indications as to specific requirements for monitoring and these must be paramount in any monitoring schedule.

CONCLUSIONS

Several materials are available to help physicians and patients with healthy food and lifestyle modifications (Pendlebury *et al.* 2007; Stauffer *et al.* 2009; Solutions for Wellness 2010). Well-designed, simple behavioral programs can produce lasting weight loss for patients with schizophrenia and improve metabolic indices, and potentially decrease significant medical risks associated with obesity with or without antipsychotic treatment

(Bushe and Paton 2005; Hoffmann *et al.* 2005; Pendlebury *et al.* 2007; Poulin *et al.* 2007; Holt *et al.* 2010).

Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Although the factors in the WGRF-16 are identified by the scientific evidence from the literature, further clinical studies are required to assess the predictive validity of the checklist in a naturalistic or randomised setting. The long-term naturalistic studies and holistic approaches show that weight management and significant lifestyle changes are attainable goals in schizophrenia patients. The authors hope that with the help of WGRF-16, the factors predicting weight gain can be assessed easily in every clinical setting and the clinicians will find it useful to the extent that all patients will be offered relevant advice and help.

DISCLOSURES/CONFLICTS OF INTEREST

Drs Tamas Treuer, Chris Bushe, Jamie Karagianis Joel Raskin and Ilya Lipkovich are employees and shareowners of Eli Lilly and Company, the manufacturer of olanzapine. In the last 3 years, Dr. John Pendlebury has received honorariums and/or advisory board fees from Eli Lilly & Company, Janssen-Cilag Ltd, Bristol-Myers Squibb and AstraZeneca; Dr Hazlin Lockman has received research grants from University Malaya and educational support and honorarium payment from Eli Lilly & Company, Janssen Cilag, AstraZeneca, Novartis, Bristol Myer Squibb and Lundbeck.

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AUTHOR CONTRIBUTIONS

In compliance with the Uniform Requirements for Manuscripts, established by the International Committee of Medical Journal Editors, the sponsor of this review did not impose any impediment, directly or indirectly, on the publication of study's results or for the contribution to the content of this manuscript. Employees of Eli Lilly and Company were involved in this review, in the collection, analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication. Drs Tamas Treuer, Chris Bushe, Jamie Karagianis, Joel Raskin and Ilya Lipkovich were involved in research activities to identify predictors for weight gain during antipsychotic treatment. Drs Lockman and Pendlebury are running behaviour intervention programs in their departments for lifestyle consultancy, complex rehabilitation and weight control and they have tremendous experience with these patients who are in risk at the initiation of treatment. The idea of this paper was born in a Solutions for Wellness Summit in Hong Kong in 10–11 June 2010, where the authors shared their practical and research experiences in the topic.

REFERENCES

1 Saha S, Chant D, McGrath J (2007) A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. **64**: 1123–1131.
2 Kisely S, Campbell LA, Wang Y (2009) Treatment of ischaemic heart disease and stroke in individuals with psychosis under universal healthcare. Br J Psychiatry. **195**: 545–550.
3 Solutions for Wellness: Personalized Program for Healthy Living (2010) Available at: http://www.solutionsforwellness.info/. Accessed 29 December 2010.
4 Treuer T, Hoffmann VP, Chen AK, Irimia V, Ocampo M, Wang G, et al (2009) Factors associated with weight gain during olanzapine treatment in patients with schizophrenia or bipolar disorder: results from a six-month prospective, multinational, observational study. World J Biol Psychiatry. **10**: 729–740.
5 Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, et al (2008) Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. **371**: 1085–1097.
6 Pendlebury J, Bushe CJ, Wildgust HJ, Holt RI (2007) Long-term maintenance of weight loss in patients with severe mental illness through a behavioural treatment programme in the UK. Acta Psychiatr Scand. **115**: 286–294.
7 Winters BD, Gurses AP, Lehmann H, Sexton JB, Rampersad CJ, Pronovost PJ (2009) Clinical review: checklists – translating evidence into practice. Crit Care. **13**: 210.
8 Holt RI, Pendlebury J, Wildgust HJ, Bushe CJ (2010) Intentional weight loss in overweight and obese patients with severe mental illness: 8-year experience of a behavioral treatment program. J Clin Psychiatry. **71**: 800–805.
9 Bushe CJ, McNamara D, Haley C, McCrossan MF, Devitt P (2008) Weight management in a cohort of Irish inpatients with serious mental illness (SMI) using a modular behavioural programme. A preliminary service evaluation. BMC Psychiatry. **15**: 76.
10 Poulin MJ, Chaput JP, Simard V, Vincent P, Bernier J, Gauthier Y (2007) Management of antipsychotic-induced weight gain: prospective naturalistic study of the effectiveness of a supervised exercise programme. Aust N Z J Psychiatry. **41**: 980–989.
11 Porsdal V, Beal C, Kleivenes OK, Martinsen EW, Lindström E, Nilsson H, Svanborg P (2010) The Scandinavian Solutions for Wellness study – a two-arm observational study on the effectiveness of lifestyle intervention on subjective well-being and weight among persons with psychiatric disorders. BMC Psychiatry. **10**: 42.
12 Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J (2009) 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet. **374**: 620–627.
13 Bushe C, Sniadecki J, Bradley AJ, Poole Hoffmann V (2010) Comparison of metabolic and prolactin variables from a six-month randomised trial of olanzapine and quetiapine in schizophrenia. J Psychopharmacol. **24**: 1001–1009.
14 Crompton D, Groves A, McGrath J (2010) What can we do to reduce the burden of avoidable deaths in those with serious mental illness? Epidemiol Psichiatr Soc. **19**: 4–7.
15 Perez-Iglesias R, Crespo-Facorro B, Martinez-Garcia O, Ramirez-Bonilla ML, Alvarez-Jimenez M, Pelayo-Teran JM, et al (2008) Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: findings of a randomized clinical trial in a drug-naïve population. Schizophr Res. **99**: 13–22.
16 Remington G (2006) Schizophrenia, antipsychotics, and the metabolic syndrome: is there a silver lining? Am J Psychiatry. **163**: 1132–1134.

17 Millen BA, Campbell GM, Beasley CM (2010) Weight changes over time in adults treated with the oral or depot formulations of olanzapine: a pooled analysis of 86 clinical trials. J Psychopharmacol. doi:10.1177/0269881110370505.
18 Enger C, Weatherby L, Reynolds RF, Glasser DB, Walker AM (2004) Serious cardiovascular events and mortality among patients with schizophrenia. J Nerv Ment Dis. **192**: 19–27.
19 Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB (2007) Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Rsearch Database. Arch Gen Psychiatry. **64**: 242–249.
20 Dean CE, Thuras PD (2009) Mortality and tardive dyskinesia: long-term study using the US National Death Index. Br J Psychiatry. **194**: 360–364.
21 Strom BL, Faich GA, Reynolds RF, Eng SM, D'Agostino RB, Ruskin JN, et al (2008) The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC): design and baseline subject characteristics. J Clin Psychiatry. **69**: 114–121.
22 Strom BL, Eng SM, Faich G, Reynolds RF, D'Agostino RB, Ruskin JN, et al (2010) Comparative Mortality Associated With Ziprasidone and Olanzapine in Real-World Use Among 18,154 Patients With Schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). Am J Psychiatry. doi:10.1176/appi.ajp.2010.08040484.
23 Bushe C, Haddad P, Peveler R, Pendlebury J (2005) The role of lifestyle interventions and weight management in schizophrenia. J Psychopharmacol. **19** (6 Suppl): 28–35.
24 Bushe C, Paton C (2005) The potential impact of antipsychotics on lipids in schizophrenia: is there enough evidence to confirm a link? J Psychopharmacol. **19** (6 Suppl): 76–83.
25 Spelman LM, Walsh PI, Sharifi N, Collins P, Thakore JH (2007) Impaired glucose tolerance in first-episode drug-naïve patients with schizophrenia. Diabet Med. **24**: 481–485.
26 Koivukangas J, Tammelin T, Kaakinen M, Mäki P, Moilanen I, Taanila A, Veijola J (2010) Physical activity and fitness in adolescents at risk for psychosis within the Northern Finland 1986 Birth Cohort. Schizophr Res. **116**: 152–158.
27 Treuer T, Karagianis J, Hoffmann VP (2008) Can increased food intake improve psychosis? A brief review and hypothesis. Review. Curr Mol Pharmacol. **1**: 270–272.
28 Case M, Treuer T, Karagianis J, Hoffmann VP (2010) The potential role of appetite in predicting weight changes during treatment with olanzapine. BMC Psychiatry. **10**: 72.
29 Lipkovich I, Jacobson JG, Hardy TA, Hoffmann VP (2008) Early evaluation of patient risk for substantial weight gain during olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective disorder. BMC Psychiatry. **8**: 78.
30 Lipkovich I, Jacobson JG, Caldwell C, Hoffmann VP, Kryzhanovskaya L, Beasley CM (2009) Early predictors of weight gain risk during treatment with olanzapine: analysis of pooled data from 58 clinical trials. Psychopharmacol Bull. **42**: 23–39.
31 Basson BR, Kinon BJ, Taylor CC, Szymanski KA, Gilmore JA, Tollefson GD (2001) Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. J Clin Psychiatry. **62**: 231–238.
32 Lipkovich I, Citrome L, Perlis R, Deberdt W, Houston JP, Ahl J, et al (2006) Early predictors of substantial weight gain in bipolar patients treated with olanzapine. J Clin Psychopharmacol. **26**: 316–320.
33 Strassnig M, Miewald J, Keshavan M, Ganguli R (2007) Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: one-year analysis. Schizophr Res. **93**: 90–98.
34 Smith E, Rothschild AJ, Heo M, Peasley-Miklus C, Caswell M, Papademetriou E, et al (2008) Weight gain during olanzapine treatment for psychotic depression: effects of dose and age. Int Clin Psychopharmacol. **23**: 130–137.
35 Kinon BJ, Basson BR, Gilmore JA, Tollefson GD (2001) Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. J Clin Psychiatry. **62**: 92–100.
36 Kinon BJ, Kaiser CJ, Ahmed S, Rotelli MD, Kollack-Walker S (2005) Association between early and rapid weight gain and change in weight over one year of olanzapine therapy in patients with schizophrenia and related disorders. J Clin Psychopharmacol. **25**: 255–258.
37 Saddichha S, Ameen S, Akhtar S (2007) Predictors of antipsychotic-induced weight gain in first-episode psychosis: conclusions from a randomised, double-blind, controlled prospective study of olanzapine, risperidone, and haloperidol. J Clin Psychopharmacol. **28**: 27–31.
38 Ujike H, Nomura A, Morita Y, Morio A, Okahisa Y, Kotaka T, et al (2008) Multiple genetic factors in olanzapine-induced weight gain in schizophrenia patients: a cohort study. J Clin Psychiatry. **69**: 1416–1422.
39 Poyurovsky M, Fuchs C, Pashinian A, Levi A, Faragian S, Maayan R, et al (2007) Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: a double-blind, placebo-controlled study. Psychopharmacology. **192**: 441–448.
40 Gothelf D, Falk B, Singer P, Kairi M, Phillip M, Zigel L, et al (2002) Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. Am J Psychiatry. **159**: 1055–1057.
41 Zipursky RB, Gu H, Green AI, Perkins DO, Tohen MF, McEvoy JP, et al (2005) Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. Br J Psychiatry. **187**: 537–543.
42 Gebhardt S, Haberhausen M, Heinzel-Gutenbrunner M, Gebhardt N, Remschmidt H, Krieg JC, et al (2009) Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. J Psychiatr Res. **43**: 620–626.
43 Saravane D, Feve B, Frances Y, Corruble E, Lancon C, Chanson P, et al (2009) Drawing up guidelines for the attendance of physical health of patients with severe mental illness. Encephale. **35**: 330–339.
44 European Medicines Agency. Summary of Product Characteristics, 2010. EMA web site. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000115/WC500055207.pdf. Accessed February 24, 2011.
45 Taylor DM, McAskill R (2000) Atypical antipsychotics and weight gain – a systematic review. Acta Psychiatr Scand. **101**: 416–432.
46 Allison DB, Casey DE (2001) Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry. **62** (Suppl 7): 22–31.
47 McIntyre RS, Trakas K, Lin D, Balshaw R, Hwang P, Robinson K, et al (2003) Risk of weight gain associated with antipsychotic treatment: results from the Canadian National Outcomes Measurement Study in Schizophrenia. Can J Psychiatry. **48**: 689–694.
48 Bushe CJ, Taylor M, Mathew M (2007) Intramuscular Olanzapine – a UK case series of early cases. Ann Gen Psychiatry. **6**: 11.
49 Hoffmann PV, Ahl J, Meyers A, Schuh L, Shults KS, Collins DM, et al (2005) Wellness intervention for patients with serious and persistent mental illness. J Clin Psychiatry. **66**: 1576–1579.
50 Hoffmann PV, Bushe C, Meyers AL, Greenwood T, Benzing L, Ahl J (2008) A wellness intervention program for patients with mental illness: self-reported outcomes. Prim Care Companion J Clin Psychiatry. **10**: 329–331.
51 Stauffer VL, Lipkovich I, Hoffmann VP, Heinloth AN, McGregor HS, Kinon BJ (2009) Predictors and correlates for weight changes in patients co-treated with olanzapine and weight mitigating agents; a post-hoc analysis. BMC Psychiatry. **9**: 12.

APPENDIX 1

WGRF-16: Weight Gain Risk Factor Checklist

Upon initiation of antipsychotic treatment
Version 1.0

Instruction to physician: Below is a list of factors that may have predictive value for substantial weight gain in patients with severe mental illness. Please read each one carefully, put an "X" in the box to indicate how much that factor describes your patient at the initiation of antipsychotic therapy and 2-3 weeks later.

16 Risk Factors

At Baseline	**YES**	**NO**
Younger age		
Male gender		
Low baseline Body Mass Index		
Non-Caucasian race		
Increased appetite		
High energy intake		
Diagnosis of undifferentiated schizophrenia		
Other medical comorbiditites		
Low social activity		
Poor patient insight		
Supervised housing conditions		
Eat until feeling full		
Poor eating habits		
Low physical activity level		

At 3rd week after treatment initiation

Improved clinical response at 3rd week of treatment		
Did your patient gain weight at the 3rd week of treatment $\geq$2 kg?		

NOTE: This WGRF-16 checklist will serve for educational and awareness purposes only, and it will not replace monitoring of patients with severe mental disorders. The presence of any of these risk factors indicates your patient is in a higher risk for gaining weight during treatment, and you should consider an intervention to help the patient avoid weight gain. Although the factors in the WGRF-16 are identified by the scientific evidence from the literature, further clinical studies are required to assess the predictive validity of the checklist in a naturalistic setting.