HHS Public Access

Author manuscript

Int Rev Psychiatry. Author manuscript; available in PMC 2019 April 15.

Published in final edited form as:

Int Rev Psychiatry. 2018 October ; 30(5): 147–154. doi:10.1080/09540261.2018.1509843.

Double jeopardy: A review of weight gain and weight management strategies for psychotropic medication prescribing during methadone maintenance treatment

Nicolas J. Schlienz, Ph.D.[1], **Andrew S. Huhn, Ph.D., M.B.A.**[1], **Traci J. Speed, M.D., Ph.D.**[2], **Mary M. Sweeney, Ph.D.**[1], and **Denis G. Antoine, M.D.**[1]

[1]Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD USA

[2]Center for Behavior and Health, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD USA

Abstract

Methadone maintenance treatment (MMT) is an important treatment tool for the opioid epidemic. One challenge is that many persons who present for MMT also have co-occurring psychiatric disorders. Individually, both methadone and psychiatric medications carry risk of weight gain. Therefore, concurrent prescribing of methadone and psychiatric medications places dual diagnosis patients at even greater risk. As a parallel obesity epidemic grows, results from clinical trials assessing weight gain and weight management strategies among MMT and psychiatric patients can both inform and guide clinical practice. Here, we review findings from a literature search for recent clinical trials that focused on weight gain and weight management strategies during MMT with concurrent psychotropic medication use. While several studies have documented weight gain during MMT and psychotropic medication treatment, we failed to identify recent work that explored concurrent prescribing. Most weight management strategies involved the use of additional medications and available data suggests that MMT and concurrent use of psychotropic medications increases the risk for obesity. More robust research is needed on weight gain and potential mitigation strategies when these treatment modalities are jointly utilized. Clarification of underlying biological mechanisms and development of non-pharmacological interventions merit further consideration.

Keywords

Opioids; Dual Diagnosis; Obesity; Methadone; Weight Gain

Corresponding Author Information: Nicolas J. Schlienz, Ph.D., Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, Telephone: (410) 550-1975, Fax: (410) 550-0030, nschlie1@jhmi.edu.

1. Introduction

In the US and abroad, the opioid epidemic has been characterized by an unprecedented number of individuals reporting abuse of and dependence on prescription pain medications and illicit opiates. In 2015, an estimated 35 million individuals used illicit opiates and prescription opioid medications worldwide (Merz, 2018; United Nations Publications, 2017), and as of 2016, opioid use disorder (OUD) rose to become the 7th leading cause of disability-adjusted life-years in the US (DALYs; US Burden of Disease Collaborators, 2018). OUD seldom occurs in isolation. Of the more than 20 million Americans with a substance use disorder (SUD), findings from the 2014 National Survey on Drug Use and Health (NSDUH) indicate that nearly 8 million individuals are dually diagnosed with a co-occurring mental illness (Center for Behavioral Health Statistics and Quality, 2015). These findings suggest treatments for OUD must therefore adopt a multi-pronged approach that considers the myriad psychiatric disorders and associated symptoms that might exacerbate the progression of OUD and/or act as a barrier to successful treatment.

Evidence-based pharmacotherapies are available for both OUD and other psychiatric disorders (i.e., anxiety, mood, schizophrenia, trauma- and stressor-related disorders). Opioid agonist therapies are effective treatments for OUD (Brady, McCauley, & Back, 2015; Connery, 2015; Schuckit, 2016), and antidepressants, mood stabilizers, and antipsychotic medications have proven successful in reducing a range of psychiatric symptoms (Maxmen, Kennedy, & McIntyre, 2008; Pincus et al., 1998). However, methadone maintenance treatment (MMT) and several classes of psychotropic medications have undesirable somatic side effects (Goldberg & Ernst, 2012; Webster, 2013) such as medication-induced weight gain.

In addition to the opioid epidemic, a global obesity epidemic has simultaneously unfolded whereby nearly 2 billion adults are currently overweight, and in the US, nearly 700 million Americans are obese. Like OUD, obesity is a contributing factor for several causes of preventable death, including heart disease, cancer, respiratory disease, and stroke (2015 Obesity Collaborators, 2017). Whereas weight gain is common to both MMT and psychotropic medication use, a growing concern is the heightened risk for weight gain among dual diagnosis patients prescribed psychotropic medications during MMT.

To the extent that individuals engaged in MMT receiving psychotropic medications for comorbid psychiatric disorders are at increased risk for weight gain, weight management emerges as a critical topic that must be openly discussed prior to and during treatment. Though MMT remains a leading treatment for OUD, evaluating the risk for weight gain and identifying strategies to mitigate this risk are essential components that inform and guide clinical practice.

In line with the series of health implications that may arise as a result of the separate and combined effects of treatment for OUD and comorbid psychopathology, the objectives of the current literature review are to summarize recent research on psychotropic medication- and MMT-related weight gain and weight management strategies and interventions. The review

concludes with a summary discussion, recognizes limitations of the existing literature, and discusses potential avenues for future research.

2. Methods

PubMed, Embase, and PsycINFO electronic databases were searched in March 2018 for randomized clinical trials (RCTs) and non-randomized clinical trials published in the past 5 years. A medical librarian assisted with the search strategy that included keywords for weight gain (e.g., body mass index), opiates (e.g., buprenorphine, methadone, naltrexone, opiate, opioid), and psychiatric medications (e.g., antianxiety, antidepressant, antipsychotic, benzodiazepine, hypnotic, mood stabilizer, sedative). The initial search strategy identified few RCTs and non-randomized clinical trials. As a result, database searches were expanded to include studies published beyond the past five years and search parameters were broadened to allow study design characteristics that resulted in initial exclusion (e.g., non-randomized). RCTs or non-randomized clinical trials involving buprenorphine and weight gain and/or weight management were not identified. Accordingly, the current literature review solely focuses on psychotropic- and MMT-related weight gain and weight management/interventions.

3. Results

3.1. Psychotropic Medication-Induced Weight Gain

Psychotropic medications are evidence-based treatments regularly utilized to alleviate a constellation of psychiatric symptoms and associated impairment. Antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase inhibitors [MAOIs], tricyclics), mood stabilizers (e.g., lithium, valproate), first generation (FGA), and second generation antipsychotic (SGA) medications have known side effect profiles and variable risk-benefit ratios (Almandil et al., 2013; Bak, Fransen, Janssen, van Os, & Drukker, 2014; Himmerich, Minkwitz, & Kirkby, 2015; Martínez-Ortega et al., 2013; Musil, Obermeier, Russ, & Hamerle, 2015). Weight gain and metabolic syndromes attributed to psychotropic medications use are well-documented concerns. The magnitude of change in body mass varies considerably between medication classes, and overall, SGAs pose the greatest risk for medication-related weight gain (Allison et al., 1999). Compared to the SGAs ziprasidone, risperidone, sertindole, aripiprazole, and asenapine, use of clozapine or olanzapine is associated with average weight gain of 4 kg during the first 10 weeks of treatment (Arterburn et al., 2016; Manu et al., 2015; Musil et al., 2015). Though increases in weight generally plateau after the first year, total gains by as much as 10 kg are not uncommon. Treatment with psychotropic medications can also occasion biochemical alterations in metabolic and lipid profiles (Himmerich et al., 2015; Pérez-Iglesias et al., 2014).

Research efforts have continued to characterize psychotropic medication-related weight gain beyond those reported in RCTs. In a retrospective chart review of patients who initiated use of SGAs, Arterburn et al. (2016) reported that instances of extreme weight gain (i.e., 7% of body weight) were common and weight gain exceeding 15% of body weight was also observed. Among patients prescribed antidepressant medications, Blumenthal et al. (2014)

conducted an electronic medical record review, and found that, compared to citalopram, the antidepressant medications amitriptyline, nortriptyline, and bupropion were associated with significantly less weight gain over 12 months of treatment; weight gain did not significantly vary between receiving the SSRI medications escitalopram, fluoxetine, paroxetine, and sertraline (c.f. Uguz, Sahingoz, Gungor, Aksoy, & Askin, 2015). In a large five-week observational study of psychotropic medications, Kloiber et al. (2015) reported that tricyclic antidepressants and mirtazapine increased body mass index (BMI) whereas SSRIs and SNRIs decreased BMI.

Empirical studies have also identified risk factors for weight gain among individuals using psychotropic medications. Cortés et al. evaluated weight and biochemical changes in patients with psychosis being treated with SGAs (Cortés, Bécker, Mories Álvarez, Marcos, & Molina, 2014). Consistent with recent reviews (e.g., Musil et al., 2015), the authors observed a significant negative association between baseline BMI and weight gain attributed to SGA treatment. In this prospective study of patients experiencing first-episode psychosis, olanzapine treatment, male gender, and lower baseline BMI values were significant predictors of weight gain in the first 3-months; at 1-year and 3-year follow-up, however, reduced social functioning was the sole significant predictor of weight gain. Similarly, a retrospective study of psychiatric inpatients conducted by Liu et al. (2014) found that greater weight at time of admission reduced the degree of weight gain and concomitant use of SGAs and mood stabilizers was also associated with weight gain. Additionally, younger age (i.e., children and adolescents), being classified as drug-naïve, female gender, and depression severity have also been identified as significant predictors of medication-induced weight gain (Kloiber et al., 2015; Musil et al., 2015; Subramaniam et al., 2014).

3.2. Weight Management Strategies During Psychotropic Prescribing

The current literature contains an array of investigations that seek to mitigate weight gain secondary to psychotropic medication. However, there are few RCTs that examine the efficacy of proposed weight gain management strategies. Our review of the literature revealed seven trials of this type, and all focused on treatment populations that were taking antipsychotic medications. Two trials explored lifestyle modification as the primary intervention and two trials evaluated metformin. The remaining three singular trials explored sibutramine, zonisamide, and ranitidine, respectively.

Trials that utilized lifestyle modification (Curtis et al., 2016; Lovell et al., 2014) were implemented in populations with recent episode(s) of psychosis. Both trials compared lifestyle interventions to treatment as usual (TAU). Curtis et al. (2016) recruited youth aged 14–25 years with first-episode psychosis (FEP) who were receiving treatment with an antipsychotic medication and evaluated a 12-week individualized intervention that included health coaching, dietetic support, and supervised exercise interventions. Compared with TAU, the treatment group was effective in attenuating weight gain. Lovell et. al. (2014) conducted an exploratory trial among individuals experiencing FEP. Over a 6-month period, the intervention group attended individual sessions that encouraged exercise and dietary changes through goal-setting and patient-led action plans, while the control group received TAU. The authors failed to observe a significant difference between treatment groups in

outcome measures including BMI and changes in waist circumference. However, sub-analysis of the 25 participants taking an antipsychotic revealed greater mean weight reduction in the intervention group and greater reduction in BMI compared with TAU.

Jarskog et al. (2013) conducted a double-blind study of overweight patients prescribed antipsychotic medications for schizophrenia or schizoaffective disorder whom were randomized to receive metformin (up to 1000 mg twice daily) or placebo. All participants received lifestyle interventions that included weekly diet and exercise counseling. Participants in the metformin arm experienced 2 kg greater weight loss than individuals in the placebo arm. Changes in fasting glucose and insulin levels did not differ between groups, however, mean decrease in HbA1C was more pronounced in the metformin group. De Silva et al. (2015) conducted a double-blind trial of South Asian patients with schizophrenia or schizoaffective disorder taking atypical antipsychotics who had gained more than 10% body weight. Participants received either 500 mg metformin twice daily or placebo for 24 weeks; all participants received verbal advice for dietary modifications and exercise. At posttreatment, a significant group x time interaction revealed that the metformin group had mean weight loss of 1.56 kg and the placebo group had mean weight gain of 1 kg. The between-group differences in BMI over time were also significant.

Biedermann et al. (2014) conducted a 24-week trial in a small sample of outpatients with schizophrenia who had gained ≥ 7% of their initial weight while on antipsychotics. Patients either received 10 mg sibutramine or placebo. At posttreatment, the sibutramine group experienced an average weight loss of 6.1 kg compared with average weight gain of 1.9 kg in the placebo group. The main significant finding was a decrease in waist/hip ratio at 12 weeks in the sibutramine group but was no longer present at posttreatment. Also, HgA1C levels significantly improved in the treatment arm by the 24-week time point. In a separate 10-week double-blind RCT, adult outpatients with schizophrenia on antipsychotics were randomized to receive either zonisamide (150 mg/day) or placebo (Ghanizadeh, Nikseresht, & Sahraian, 2013). The study found significant changes between the two groups in both BMI and waist circumference. Two of the three trials of metformin were based in the outpatient setting. The only hospital-based study that was identified (Mehta & Ram, 2016) involved an RCT of adult inpatients with schizophrenia randomized to receive either daily olanzapine and ranitidine (150 mg), twice daily olanzapine and ranitidine (150 mg), or olanzapine alone for 8 weeks. No significant between-groups differences in weight gain were observed at the 4- or 8-week time points. Overall, the trials evaluating metformin, sibutramine, and zonisamide yielded positive findings. However, the potential for drug-interactions with MMT and other medications increases the need for research on non-pharmacological interventions.

3.3. Weight Gain in Methadone Maintenance Therapy

Methadone maintenance therapy (MMT) is a commonly used and effective treatment for OUD, however, weight gain among patients is relatively common. In some instances, moderate increases in weight associated with MMT may be considered acceptable. For example, because active heroin use is associated with some weight loss, individuals who are actively using heroin prior to entering MMT may present as underweight (Alves, Costa, &

Custódio, 2011). On the other hand, weight gain during MMT that represents a shift from normal BMI to overweight or obese may be problematic for cardiovascular risk.

Relatively few studies and no RCTs have reported on weight gain during the course of MMT, although research on this topic has yielded similar results. A study of 23 methadone patients in Israel reported a significant increase in BMI from a mean of 24.0 ± 4.2 upon initiation of methadone treatment to 25.7 ± 4.0 at 6-month follow-up and 27.1 ± 4.8 at 12-month follow-up (Peles, Schreiber, Hetzroni, Adelson, & Defrin, 2011). A second study of 109 MMT patients in Israel found that BMI increased significantly from a mean of 22.5 ± 3.8 to 24.4 ± 4.3 over the course of methadone dose stabilization (mean duration = 270 ± 168 days; Peles, Schreiber, Sason, & Adelson, 2016). Patients in the latter study were more likely to gain weight if they were negative for hepatitis C, had a negative drug screen for benzodiazepines, or had a positive drug screen for THC upon admission. Whereas Peles et al. (2016) did not find sex to be a significant risk factor for weight gain among MMT patients, a study by Fenn, Laurent, and Sigmon (2015) found that women tended to gain more weight relative to men. Fenn et al. (2015) examined BMI at MMT intake and a subsequent follow-up (mean 1.8 ± .95 years post-intake) and observed BMI increases from 27.2 ± 6.8 to 30.1 ± 7.7. BMI increase was, on average, approximately 10% of body weight, although women in the study gained weight more rapidly (17.5% increase in body weight). A study of MMT patients in Bratislava, Slovakia found that patients tended to be underweight compared to the Slovakian population mean upon treatment entry (Okruhilca and Slezakova, 2008). Akin to other findings, BMI increased over the course of one year of MMT. Even so, after one year of MMT, patients were still slightly below the distribution of BMI for the Slovakian population (Okruhilca and Slezakova, 2008). Although some studies described above may have included underweight participants whose weight gain was generally favorable, overall mean BMI increases may represent problematic weight gain for those patients entering treatment with normal or excess weight.

While observational studies that characterize weight gain during MMT are relatively consistent, there are no RCTs examining weight gain during MMT in comparison to other opioid treatment options, such as buprenorphine, naltrexone, or supervised withdrawal with no ongoing medication assisted treatment. One chart review compared weight gain in 16 MMT patients relative to 20 naltrexone-treated patients at 3 months and 6 months relative to baseline prior to maintenance (Mysels, Vosburg, Benga, Levin, & Sullivan, 2011). The study did not detect significant changes in weight across time in treatment and did not observe differences between groups, but the small sample size and likelihood of systematic variation in other dimensions of treatment between MMT and naltrexone (e.g., different staff, treatment procedures) prevent definitive conclusions.

3.4. Weight Management Strategies During MMT

Few studies describing weight gain in MMT patients have examined strategies to prevent weight gain or described modifiable protective factors against weight gain in this population. Peles et al. (2016) reported that MMT patients with higher BMI values reported poor dietary habits and greater preference for sweet foods relative to lower BMI patients. Although correlational, these data link higher BMI among MMT patients with unhealthy dietary

practices, suggesting that dietary modification is a reasonable point of intervention. Other studies have shown a tendency toward poor nutrition among methadone patients, including insufficient consumption of fruits, vegetables, and grains (Alves et al., 2011) and increased consumption of sweets, snacks, or "junk" foods relative to control participants (Nolan & Scagnelli, 2007; Zador, Lyons Wall, & Webster, 1996). Further, Richardson and Wiest (2015) observed a trend for increased nutritional risk as assessed by the "Determine Your Nutritional Health" survey, which was associated with decreased treatment retention in MMT patients.

Taken together with problematic weight gain associated with methadone, these data indicate that nutritional interventions may be necessary and helpful within MMT patients. To that end, Sason, Adelson, Herzman-Harari, & Peles (2018) randomly assigned methadone maintenance patients to receive a brief behavioral intervention involving nutrition education and weight monitoring or to a control group where weight was monitored while receiving TAU. The intervention was effective at improving nutrition knowledge but did not alter BMI over the brief six-week monitoring period. A longer duration of monitoring following the nutritional intervention may have been necessary to detect any long-term preventive effects on weight gain. Overall, implementing nutritional assessments and interventions within OUD treatments may be a promising future direction of non-pharmacological treatment strategies (Jeynes & Gibson, 2017; Wiss, Schellenberger, & Prelip, 2017; Wiss & Waterhous, 2014).

4. Discussion

The aim of this manuscript was to review the recent literature for clinical trials on weight gain and weight management strategies during concurrent MMT and use of psychotropic prescription medications. No trials of concurrent prescribing were found that characterized weight gain and weight management techniques in the presence of MMT and psychotropic medications individually. Within the trials reviewed, the majority of psychotropic medication trials focused on weight gain and weight management strategies for 2GAs. There were several studies that examined weight gain during MMT. Conversely, there was only one study that examined weight management strategies during MMT and did not report significant findings.

With weight gain becoming an increasing concern in MMT, the dearth of recent RCTs discussed in the current review prompts multiple recommendations for future research endeavors. At a minimum, future RCTs involving MMT or psychotropic medications should include weight and lifestyle measures regardless of whether weight is a primary outcome variable of interest. Future research should also focus on other drug classes (e.g. antidepressants) and comparative studies of drugs within each class should be implemented (e.g. sertraline vs paroxetine, methadone vs. buprenorphine vs. naltrexone). Where weight differences are found, investigations should be conducted to identify whether these changes modify any biological markers such as A1C.

Though beyond the scope of this review, the causal mechanisms of weight gain during MMT are unclear and likely multifactorial. Weight gain during MMT may be directly attributable

to methadone, including changes in sweet taste preference or glycemic dysregulation with chronic opioid exposure (Mysels et al. 2010). Further, it may be the case that individuals in early recovery tend to eat a high calorie diet to compensate for the downregulation of neural reward systems that occurs during the course of active OUD (Kelley & Berridge, 2002). Further investigation is required to clarify the interplay between these biological and non-biological mechanisms and to determine proper interventions.

The majority of RCTs for weight management focused on medications. Indeed, some of these trials demonstrated significant findings. However, increasing the medication burden in this population opens the possibility for drug-drug interactions and suboptimal outcomes. Therefore RCTs of non-pharmacological techniques should be considered in the future just as they have been in other clinical domains (Harris et al., 2016).

While research in dual diagnosis populations is complex due to ongoing OUD and other psychiatric illness needs, weight gain outcomes and management strategies in this population merit further investigation as dual diagnosis patients are at risk for more negative outcomes than those with OUD alone (Ponizovsky, Rosca, Haklai, & Goldberger, 2015).

Effective treatments are available for both OUD and co-occurring mental illness, and these modalities will be invaluable in the ongoing opioid epidemic. However, our findings demonstrate that practitioners should be mindful of potential additive effects on weight gain when prescribing psychotropic medications during MMT. Ultimately, it will also be important to create financially sustainable ways for program administrators to incorporate effective practices for weight management into MMT to elevate the standard of care for MMT patients.

Acknowledgements

The authors would like to thanks Julie Nanavati for assistance with the literature search.

Disclosure Statement

The authors report no conflicts of interest. The National Institute on Drug Abuse (NIDA) provided financial support for the participation of Dr. Schlienz and Dr. Huhn (T32-DA07209) and for Dr. Antoine (K24-DA023186). The authors alone are responsible for the content and writing of the paper.

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