Comparison of Weight Changes in Patients Treated with Different Antidepressants: Clinical Experiences in Taiwanese Patients

Jian-An Su, MD; Hin-Yeung Tsang, MD, PhD

Background: Psychiatric patients are more likely to gain weight when prescribed antipsychotics or antidepressants. Studies on these issues in Taiwan are scarce. This study compared weight changes in patients treated with NaSSA (Noradrenergic and Specific Serotonergic Antidepressant) and SSRIs (Selective Serotonin Reuptake Inhibitors), and investigated possible associated factors.

Methods: An observational, non-randomized study was conducted on all patients diagnosed with depression attending the out-patient’s clinic at a general hospital. Patients treated with NaSSA or SSRIs were monitored for 24 weeks.

Results: Forty-Seven patients (27 patients on NaSSA and 20 on SSRIs) completed the study. Patients taking NaSSA gained an average of 1.87 kg (SD: 4.14, median: 1.0, range: -3.5 to 11.0) at the end of the study, compared to 1.83 kg (SD: 3.78; median: 1.5, range: -7.0 to 8.0) for the SSRIs group. No statistically significant difference existed between the two groups. However, patients who had never previously been treated with either SSRIs or NaSSA exhibited significantly greater weight gain (4.84 kg, SD: 3.20, median: 4.75, range: 0 to 11.0) than those who had previously been treated (-0.78 kg, SD: 2.36, median: -0.5, range: -7.0 to 3.5). Low initial body mass index and concomitant medications also seemed to be linked to weight gain.

Conclusion: Significant weight gain occurred in those patients who had not been previously treated with NaSSA or SSRIs. Patients should be informed of this possibility before initiating treatment, especially those with low body mass index and those prescribed co-medications. Furthermore, the treatment program should include weight monitoring, nutritional assessment and counseling.

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Key words: Antidepressant, NaSSA, SSRIs, body weight.

Psychiatric patients are more likely to gain weight when taking psychotropic agents. Weight gain following medication may in turn influence drug compliance even given a favorable clinical response. More importantly, significant weight gain may contribute to metabolic syndrome, which...
in turn may cause severe medical problems and high mortality.\(^5\)\(^6\)

Amongst psychotropic agents, second generation antipsychotics and mood stabilizers have been reported to lead to significant weight gain during treatment.\(^3\) Antidepressants also have the same effect though only a handful of studies have focused on this issue.

Selective serotonergic reuptake inhibitors (SSRIs) were first marketed in the late 1980s. SSRIs rapidly replaced traditional tricyclic antidepressants (TCA) because of their favorable side effect profile\(^7\)-\(^9\) and soon became the most common regimens for treating depression.\(^10\) Studies focusing on weight change associated with SSRIs claimed that SSRIs were “weight neutral”, meaning that they do not affect body weight during treatment.\(^11\) However, subsequently developed SSRIs, such as paroxetine, were found to significantly promote weight gain.\(^12\)\(^13\) The mechanisms involved in these weight changes are still being debated and their pathophysiology continues to be studied.\(^11\)

Mirtazapine, which has been licensed for treating depression in Taiwan since late 2001, has a different mechanism than SSRIs. Mirtazapine enhances noradrenergic and serotonergic transmission by blocking presynaptic \(\alpha_2\) hetero- and auto-receptors.\(^14\) It is suggested that the blockade of \(H_1\) receptor, which may increase appetite, is associated with weight gain.

Masand (2001) assessed the relative risk of weight gain between main classes of antidepressants.\(^15\) The analytical results demonstrated that mirtazapine has the highest risk of causing weight gain, followed by TCAs and SSRIs. Studies of weight gain in patients taking mirtazapine proved controversial. Krasus et al. (2002) reported that their patients had a mean weight gain of 2.4 kg following four weeks of treatment.\(^16\) Another long-term study demonstrated that patients gained 2.5 kg in an open label study lasting 8-12 weeks, after which all of the subjects entered a double blind study lasting 40 weeks. At the end of the study, body weight gain was 1.4 kg.\(^17\) Moreover, a placebo controlled trial (study period: six weeks) reported no significant difference between mirtazapine and amitriptyline (a TCA) but found that both drugs were associated with greater weight gain than the placebo group.\(^18\) Weight changes associated with the use of SSRIs to treat depression have not been investigated as much.\(^19\)

Michelson et al. (2000) reported that patients exhibited reduced body weight only during the initial four weeks of fluoxetine treatment, and subsequently gained an average of around 3 kg following 50 weeks of treatment.\(^19\) They concluded that no significant difference existed between the fluoxetine and placebo groups. However, different SSRIs appear to impact weight change differently. Fava et al. (2000) reported that paroxetine was associated with more significant weight gain (approximately 3.6%) compared to the baseline. Additionally, the percentage of significant weight gain (defined as having more than 7% weight gain following treatment) was also higher for paroxetine (25.5%) than fluoxetine (6.8%) and sertraline (4.2%).\(^12\)\(^13\) In contrast, an average weight decrease of 0.2 kg occurred following six weeks in the paroxetine-treated group, while weight gain of 1.1 kg occurred in the mirtazapine-treated group.\(^20\) An independent investigation also found only minimal weight gain in mirtazapine-treated patients (mean: 0.8 kg, SD: 2.7) and slight weight loss in fluoxetine-treated patients (mean: -0.4 kg, SD: 2.1).\(^21\)

Weight changes in patients taking antidepressants have not been fully investigated in Taiwan. To our knowledge, only one previous case report exists regarding mirtazapine-induced weight gain.\(^22\) Consequently, an urgent need exists for clinical studies on patients treated with antidepressants, particularly mirtazapine and SSRIs. The aims of this study included (1) comparing weight changes between patients treated with mirtazapine, a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA) and SSRIs, (2) investigating possible factors associated with weight changes during the treatment period, and (3) detecting differences between those previously treated and not previously treated with antidepressants (either SSRIs or mirtazapine).

**METHODS**

This observational, non-randomized study was conducted between 2004 and 2005. All patients were diagnosed (by one senior psychiatrist and according to DSM-IV) with depressive disorders (including major depressive disorder, dysthymic disorder, bipolar depression, adjustment disorder with depressive mood, depressive disorder due to general medical condition and depressive disorder NOS) and were
treated in the out-patient’s department of a general hospital. Additional inclusion criteria were that the subjects had to be at least 18 years old, taking either SSRIs (including fluoxetine and paroxetine) or an NaSSA (mirtazapine), and willing to take part and be regularly followed up for 24 weeks. Exclusion criteria were terminating the treatment prematurely, or changing the regimen because of side effects or poor clinical response.

Demographic data and regimen were gathered. Height was measured initially using physician’s scales (model KC-21C; Kain-Chung Scale Factory Co., Tainan, Taiwan). Body weight was measured using the same apparatus, with subjects wearing light indoor clothes, at the beginning of the study and on each follow up visit. Body mass index (BMI) and weight change were calculated at the baseline and following 24-weeks of treatment. For patients who had previous experience of taking antidepressants before being enrolled in the study, the duration of previous antidepressant treatment was also recorded.

Paired t-test and independent sample t-test were applied to continuous variables, while chi-square tests were used for categorical variables. A \( p \) value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS for Windows software (version 10.0).

**RESULTS**

Forty-seven patients (27 patients taking an NaSSA and 20 patients taking SSRIs) completed this observational study. Demographic data, weight, initial BMI and weight change at the baseline and following 24-weeks of treatment are listed in Table 1. The NaSSA- and SSRI-treated groups did not differ significantly in terms of gender, age, initial and final weight, or initial BMI. Weight change in the NaSSA-treated group at the end of treatment was 1.87 kg (SD: 4.14; median: 1.0, range: -3.5 to 11.0) compared with 1.83 kg (SD: 3.78; median: 1.5, range: -7.0 to 8.0) in the SSRI-treated group. Although slight weight gain occurred in both groups at the end of the study, this gain was not statistically significant. Six patients (22.2%) in the NaSSA-treated group and five patients (25%) in the SSRI-treated group exhibited a weight gain at the end of the study that exceeding 7% of their body weight.

To determine whether any difference existed between those who had or had not previously received antidepressants, the subjects were divided into two groups: “antidepressant naive” group (n = 22) and “previously exposed” group (n = 25). “Antidepressant naive” referred to those who had never previously been treated with either NaSSA or SSRIs, while the term “previously exposed” referred to those already receiving either NaSSA or SSRIs when they were enrolled in the study and were simply continuing the same regimen for another 24 weeks. The average duration of taking antidepressants in the previously exposed group was 10.03 months (S.D: 7.60, range: 3 to 33 months). The antidepressant naive group displayed significant weight gain (4.89 kg, SD: 3.76 and 4.78 kg, SD: 2.37, respectively). However, in the previously exposed group, slight weight loss was identified in both the NaSSA- and

### Table 1. Demographic Data and Weight Changes of NaSSA- and SSRI-Treated Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NaSSA (N = 27)</th>
<th>SSRIs (N = 20)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (59.3%)</td>
<td>10 (50%)</td>
<td>0.528</td>
</tr>
<tr>
<td>Male</td>
<td>11 (40.7%)</td>
<td>10 (50%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58.6 ± 14.3</td>
<td>50.2 ± 10.3</td>
<td>0.294</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Week 0</td>
<td>58.70 ± 9.47</td>
<td>61.22 ± 14.78</td>
<td>0.148</td>
</tr>
<tr>
<td>At Week 24</td>
<td>60.69 ± 9.85</td>
<td>63.05 ± 14.01</td>
<td></td>
</tr>
<tr>
<td>BMI at Week 0</td>
<td>23.20 ± 2.40</td>
<td>23.59 ± 5.18</td>
<td>0.731</td>
</tr>
<tr>
<td>BMI at Week 24</td>
<td>23.44 ± 3.10</td>
<td>24.32 ± 4.88</td>
<td>0.622</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>1.87 ± 4.14</td>
<td>1.83 ± 3.78</td>
<td></td>
</tr>
<tr>
<td>Weight gain ≥ 7%</td>
<td>22.2% (n = 6)</td>
<td>25% (n = 5)</td>
<td>0.824</td>
</tr>
</tbody>
</table>

**Abbreviations:** NaSSA: noradrenergic and specific serotonergic antidepressant; SSRIs: selective serotonin reuptake inhibitors; BMI: body mass index.
SSRI-treated patients (-0.93 kg, SD: 1.94 and -0.59 kg, SD: 2.90, respectively). Within group comparison (week0 versus week24) and between group comparison (NaSSA versus SSRIs) revealed no statistically significant differences.

Subjects who exhibited weight gains exceeding 7% of their initial weight (defined as significant weight gain) were further analyzed to examine any association with age, gender, initial BMI, classes of medication and co-medications. Co-medications were defined as antipsychotics or mood stabilizers. A total of 11 patients, all in the antidepressant naive group, displayed a weight gain at the end of the study that exceeded 7% of their initial weight (Table 4). Significant weight gain was associated with low initial BMI and co-medications (Table 4 and Table 5) but not with gender, age or class of antidepressants (NaSSA or SSRIs).

DISCUSSION

The results of this study demonstrated that both NaSSA- and SSRI-treated patients exhibited slight weight gain following 24 weeks of treatment. This study found no evidence that patients treated with SSRIs initially demonstrated weight loss followed by a larger weight gain during follow-up.10,11 Weight gain following treatment with antidepressants may

![Fig. 1. Weight change in “antidepressant naive” and “previously exposed” group.](image)
indicate (1) recovery from depression with associated appetite improvement; or (2) antidepressant-induced weight gain; or (3) patients remaining depressed but with atypical features and reversed vegetative signs. Due to these complicated interactions and the study design, the results of this study are not intended to explain the causal relationship between antidepressants and weight gain. It is important to clarify that this study was focused on weight changes following antidepressant medication, something rarely reported in Taiwan.

Certain clinical parameters, such as age, gender, initial BMI, smoking history, clinical response and dosage, were found to be related to weight change following psychopharmacologic treatment. However, the analytical results indicated significant weight gain in patients with lower initial BMI but no relationship to age and gender. Other studies also support this finding. The power to predict future weight gain associated with these parameters remains controversial. Some studies have found evidence that female and young patients were vulnerable to gaining weight when using psychotropic agents. However, the results of this study did not support this phenomenon. Another possible explanation is that the sample size in this study was too small to exhibit statistically significant differences. Future large-scale studies are required to clarify the relationship between these clinical parameters and medication-associated weight gain.

Interestingly, significant weight gain occurred in the subjects who had never previously been treated with either NaSSA or SSRIs (antidepressant naive group). A similar finding was also reported by Thase et al. (2001), who found that patients gained 2.5 kg during 8 - 12 weeks of treatment with NaSSA reducing to a further weight gain of just 1.4 kg during the following 40 weeks of observation. Meta-analysis revealed that most of the weight gain associated with mirtazapine was experienced during the first four weeks of treatment. Weight gain appears problematic during the acute phase of treatment with either NaSSA or SSRIs but not during long-term therapy. One of the explanations for this phenomenon might be that disturbed appetite, sleep and low mood initially respond well to antidepressants. In contrast, body weight in those who had previously been exposed to either NaSSA or SSRIs had reached a plateau, as the patients underwent long-term treatment. Additionally, psycho-education regarding the possible hazard of weight gain might be initiated when the patients' mood improves, which might help prevent excessive weight gain. However, no hard evidence exists supporting a "switching point" between continuous weight gain and plateau in individuals who have recently started antidepressant therapy. Our study demonstrated that weight gain may take more than six months to plateau (Fig. 1).

The U.S Food and Drug Administration (FDA) defines significant weight gain associated with drug treatment as a gain exceeding 7% of the original weight following treatment. Sussman et al. (2001) found that 17.9% of SSRI-treated patients gained more than 7% of weight in a pooled analysis. Significant weight gain was also seen after long-term treatment with paroxetine, an SSRI (25.5%), and mirtazapine, an NaSSA (12.7%). This study found 22.2% (6/27) of subjects in the NaSSA-treated group and 25% (5/20) of those in the SSRI-treated group exhibited weight gain exceeding 7% following 24

### Table 4. Factors Possibly Related to Significant Weight Gain

<table>
<thead>
<tr>
<th></th>
<th>Weight gain &lt; 7%</th>
<th>Weight gain &gt; 7%</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaSSA</td>
<td>21 (58.3%)</td>
<td>6 (54.5%)</td>
<td>0.824</td>
</tr>
<tr>
<td>SSRIs</td>
<td>15 (41.7%)</td>
<td>5 (45.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (44.4%)</td>
<td>5 (45.5%)</td>
<td>0.953</td>
</tr>
<tr>
<td>Female</td>
<td>20 (55.6%)</td>
<td>6 (54.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>55.19 ± 12.50</td>
<td>54.36 ± 16.23</td>
<td>0.858</td>
</tr>
<tr>
<td><strong>Initial BMI</strong></td>
<td>23.99 ± 3.72</td>
<td>21.32 ± 3.40</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Co-medications</strong></td>
<td>N = 6 (6/36, 16.7%)</td>
<td>N = 7 (7/11, 63.6%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Abbreviations:** NaSSA: noradrenergic and specific serotonergic antidepressant; SSRIs: selective serotonin reuptake inhibitors; BMI: body mass index

### Table 5. Factors Related to Weight Change

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% C.I)</td>
<td>p value</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>0.86 (0.22-3.34)</td>
<td>0.824</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>1.04 (0.27-4.05)</td>
<td>0.953</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>1.00 (0.95-1.05)</td>
<td>0.854</td>
</tr>
<tr>
<td><strong>Initial BMI</strong></td>
<td>0.75 (0.57-0.98)</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Co-medications</strong></td>
<td>8.75 (1.94-39.57)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI: body mass index; OR: odds ratio; C.I: confidence interval
weeks of treatment. Among these 11 patients, 63.6% (7/11) were also taking other medications (co-med-
ications). In contrast, only 16.7% (6/36) of the sub-
jects who gained less than 7% of their initial weight were taking co-medications, specifically antipsy-
chotics or mood stabilizers. The evidence indicates that synergic effects in weight gain may occur if antipsychotics or mood stabilizers are prescribed with antidepressants.

This study has several limitations. First, the study was an open-labeled, observational, non-
randomized design in which selection bias was unavoidable. However, this design may also reflect the reali-
ty of clinical practice. Second, the sample size was relatively small, creating a possibility of type II error. Third, the severity of depression was not considered. Fourth, comorbidity with other psychiatric or physi-
cal condition(s) complicated the prescription and was not considered in the statistical analyses. Finally, although all of the patients followed the recommend-
ed dosage of antidepressants, the dosage was not fixed and was adjusted according to clinical response. This also reflects clinical practice but the influence of different dosages was not considered in the analyses. Further investigation using a more sophisticated design is necessary to obtain data that can be generalized to all patients diagnosed with depression.

Despite the above limitations, the results of this study provide valuable clinical information about weight gain in Taiwanese patients with depression receiving NaSSA or SSRIs.

In conclusion, weight gain is a significant prob-
lem with both NaSSA and SSRIs during the initial phase of treatment but not for long-term treatment. The magnitude of weight gain in both the NaSSA-
and SSRI-treated groups does not differ significantly between short- and long-term treatments. Additionally, low initial BMI and augmentation with other psychotropic agents are associated with weight gain following 24-weeks of treatment.

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isms underlying drug-induced weight gain in psychiatric
比較使用不同抗憂鬱劑的體重變化：台灣病人的臨床經驗

蘇建安 曾憲洋

背景：精神疾病不只在使用抗精神病藥物時會有體重增加的現象，在使用抗憂鬱劑時也有此情況；但是這方面的研究在台灣卻是比較缺乏。本研究的目的是在比較 NaSSA 和 SSRIs 這兩類抗憂鬱劑對體重的影響以及可能的相關的因子。

方法：這裡是一個觀察性、非隨機性的研究。所有病患均是在門診治療的憂鬱症患者，服用 NaSSA 或 SSRIs 其中一種抗憂鬱劑，且可以配合規則服用跟持續 24 週的門診追蹤。

結果：一共有 47 位病患完成此研究，27 位病患服用 NaSSA，20 位病患服用 SSRIs。服用 NaSSA 這組病人體重增加 1.87 公斤（標準差：4.14；範圍：-3.5~11.0；中數：1.0）；服用 SSRIs 這組則增加 1.83 公斤（標準差：3.78；範圍：-7.0~8.0；中數：1.5）；兩組在體重增加上並無統計上的差異。然而，在之前從未服用過 NaSSA 或是 SSRIs 的病人，跟之前已經在服用 NaSSA 或是 SSRIs 的病人相比，前者有顯著的體重增加（平均：4.84 公斤；標準差：3.20；範圍：0~11.0；中數：4.75），而後者的體重只有輕微減少（平均：-0.78 公斤；標準差：2.36；範圍：-7.0~3.5；中數：-0.5）。此外，治療前的 BMI (body mass index) 值以及是否合併使用其他藥物與體重增加有高度相關。

結論：無論是使用 NaSSA 或是 SSRIs 治療的病人，如果之前從未曾服用過此類藥物，則體重會有相當明顯的增加；而在之前已經服用此類藥物一段時間的病患卻無此現象。因此，在處方 NaSSA 或 SSRIs 等藥物前，應先告知病人體重增加的可能；特別是那些 BMI 在治療前比較低，同時合併使用其他藥物的病人。此外，使用這類藥物的病人，其治療計劃應包括體重的監控、營養狀況的評估和諮詢，以避免因體重增加而併發其他的身體疾病。

（長庚醫誌 2006;29:154-61）

關鍵字：抗憂鬱劑，NaSSA，SSRIs，體重。