Do Newer Antidepressant Drugs *Really* Have Reduced Side Effects? Examining a Random "Real World" Sample of 300+ Receivers of Medications

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Abstract

Newer antidepressant drugs are frequently cited as having reduced side effect profiles to that of their older counterparts. However, recent studies have begun to dispute this claim, citing selective sampling, short clinical trials, and clinical trial environments as influencing reported outcomes. At present, little research on antidepressant side effects draws on RWD (Real-World Data). Despite this, interest in examining RWD samples for antidepressant drug side effects is increasing as of 2020. The reported study asked a random sample of 300+ individuals taking a variety of different antidepressant medications to complete online drug side effect self-report scales with previously high validity. Newer antidepressants belonging to the atypical antidepressant drug class were reported as having only slightly reduced side effects of weight gain compared with older SSRI-class medications. No reduced side effects of increased depression, anxiety, sexual dysfunction (SD), sleepiness, or suicidal ideation (SI) were found for the newer atypical-class medications vs older SSRI-class agents. Medication adherence did not differ significantly between SSRI and atypical classes. No evidence for reduced side effects was found for newer SSRI and atypical antidepressants vs older same-class drugs when comparing six new and old medications drawn from atypical and SSRI classes. However, atypical antidepressants were associated with increased use of adjunct medications to bolster primary treatment.

Keywords: Antidepressant tolerability, Non-clinical study, RWD (Real-World Data), Social P v, SSRI-atypical side effects comparison

Introduction

Antidepressant medications are some of the most prescribed groups of drugs in the developed world (Corponi et al. 2020). Their therapeutic use is defined as treating disorders involving prolonged or chronic episodes of low mood. The British National Formulary (BNF) group antidepressants into four main classifications, based upon proposed pharmacological mechanism of action (MOA). Classifications are: Monoamine-oxidase inhibitors (MAOIs); Tricyclic and related (TCAs); Selective serotonin re-uptake inhibitors (SSRIs) and a final, newer class defined as "atypical". Notable is that proposed MOAs for the "atypical" group can vary significantly between drugs (Nelson, 2019). While all classes of established and newer antidepressants may successfully treat depression, negative side effects remain the most serious historic and contemporary barriers to medication compliance (DePetro, 2020).

In the UK, the most commonly prescribed medications for depression now belong to the SSRI and atypical medication classes. Less frequently are older TCA or (rarely) MAOI medications prescribed, due to concerns of safety and tolerability (Stahl, 2011). Pharmaceutical companies research and development goals now focus on developing new SSRI and atypical medications for reasons of reduced side effects, while maintaining established treatment efficacy (Krystal et al. 2020). While it is periodically claimed some newer antidepressants achieve this goal (Witkin, 2020), some scholars argue it remains unclear whether many specific newer drugs, or newer classes of drugs are any better tolerated than previously existing medications in a real-world setting independent of controlled trials (Healy, 2018; Healy & Cattell, 2003; Montejo et al. 2019). While newer-class SSRI and atypical antidepressants are often proposed to have reduced side effects vs older medications, troubling side effects of depression, anxiety, sexual dysfunction, sleepiness, weight changes, and suicidal ideation are regularly still reported as leading causes of treatment discontinuation in real-world studies (See DePetro, 2020; Healy, 2018; Jacobsen et al. 2020; Montejo et al. 2019).

The widest body of evidence for reduced side effects in common newer vs older antidepressant medications comes from clinical trials. For example, the newer atypical drug Desvenlafaxine (2007) proposes fewer side effects and greater tolerability than its atypical predecessor; Venlafaxine (1993). A manufacturer-affiliated review (Reddy et al. 2010) demonstrated Desvenlafaxine as highly effective for depression, whilst carrying a low incidence of side effects. However, the side effects reported for Desvenlafaxine were comparable to profiles of other SNRI (atypical) drugs, with no differences found for side effects such as weight gain and anxiety. Several studies illustrate Desvenlafaxine has favourable outcomes when compared with placebo in depressed individuals (DeMartinis et al. 2007; Liebowitz, Yeung & Entsuah, 2007; Septien-Velez et al. 2007). However, for some studies (i.e. DeMartinis et al. 2007) primary endpoints of depression scales (HAM-D17) are powered to measure a reduction in depression scores only and not the >50% selective improvement measure uniformly recommended for antidepressant drug research (See Koda-Kimble et al. 2004). By explanation, Desvenlafaxine's response rate appears 40-60% – lower than common benchmarks for acceptable antidepressants, which typically score between 65-75% (See Healy, 2018). The study lasted only eight weeks, despite National Institute for Clinical Excellence (NICE) prescription guidelines indicating acute phase of MDD (Major Depressive Disorder) typically lasts at least 12 weeks (See Clark, 2011). While some research exploring anxiety-response in mice has been conducted recently (Patil et al. 2020), no independent human head-to-head studies examining Venlafaxine and Desvenlafaxine presently exist, making it difficult to evidence any suggestions of improved tolerability for the newer atypical antidepressant.

Similarly, the newer SSRI Escitalopram is often suggested as more tolerable that its older SSRI counterpart Citalopram. Trkulja (2010) conducted a meta-analysis of existing head-to-head clinical trials comparing efficacy and tolerability of older SSRI Citalopram vs the newer SSRI Escitalopram, noting many studies of treatment tolerance concluded at the eight-week mark. In reviewing drop-out and discontinuation rates due to intolerable side effects in seven double-blind studies – where treatment ranged for four-weeks to twenty-four-weeks – Trkulja (2010) found no statistically significant difference in side effects between patients treated with either Citalopram or Escitalopram. A similar analysis by The Cochrane Group also concluded no significant differences in both total adverse effects and individual adverse effects in a head-to-head comparison (Santilli et al. 2009). Trkulja, (2010) highlights the problematic methodological underpinnings of many same-class drug tolerability studies. For example, an oft-cited study by Yevtushenko et al. (2007) upholds clear benefits of reduced side effects for Escitalopram vs Citalopram. However, Escitalopram tolerability was determined by recording of patient adverse events raised in interview with investigators. This is despite study design otherwise utilising robust and established quantitative scales in a six-week outpatient setting to measure aspects of efficacy.

Other studies position contradicting findings; researchers often suggesting newer atypical-class antidepressants may overall have improved medication adherence compared with SSRIs, due to their predicted reduced side effect profiles. Foley, DeSanty & Kast (2006) found the newer atypical antidepressant Bupropion to have a very low incidence of sexual dysfunction as a side effect, when considering the well-documented sexual side effects of SSRI medications. Similarly, scholars highlight atypical drugs Bupropion and Venlafaxine, and the newer-SSRI Escitalopram as particularly side effect sparing (See Cipriani et al. 2009; Sanchez et al. 2003). Others have claimed Escitalopram (2003) presents reduced side effects of anxiety/stimulation and insomnia compared with Citalopram (1989) (See Cipriani et al. 2009; Einarson, 2004). However, converse findings are also available. Montejo et al. (2001) found the atypical drug Venlafaxine had a higher incidence of sexual dysfunction compared with same-class drugs, and even some SSRIs (Sertraline, Fluvoxamine). Similarly, the atypical medication Mirtazapine has been well-evidenced as an appetite stimulant (Stahl, 2011), and the same-class atypical Bupropion shown to be an appetite suppressor (Stahl, 2011), suggesting conflicting claims regarding blanket reduced incidence of weight-change side effects for the newer atypical drug class.

Some scholars suggest clinical trial study design and methodologies lend to selective results that inflate increased tolerability claims (See Healy, 2018; Healy & Cattell, 2003). Such thinking highlights that enduringly positive "low-side effect" data presented in clinical trials for newer-class and newer-medications often comes with the caveat of being difficult to replicate, with trial subjects often displaced from their regular routines, interactions and environments. Sometimes, clinical examinations run only for a short time. Healy (2018) and Lorenz (2019) question whether clinical trials run long enough to define between short and long-term, mild, and severe side effects. They argue short drug trials recurrently highlight mild antidepressant side effects, due to not allowing time for lasting side effects to manifest to a recognisable, or reportable level. This is opposite to evaluating side effects when medication receivers have continued treatment over a longitudinal timeframe, during their everyday lives (Jacobsen et al. 2020; Montejo et al. 2019). Such debate represents a prominent research gap, highlighting the rarity of impartial self-report studies that examine random "real world" samples. This study's novel design collected antidepressant side effect data directly from participants already taking antidepressants, using side effect scales previously showing high validity in clinical settings. Reported data exceeded the "low-limit" of 8-weeks and "upper-

limit" of 24-weeks commonly seen in side effect trials, with most participants taking primary medication for at least 6 months. This promoted accurate self-reporting of data, increasing reliability and validity of outcomes by examining first-hand, real-world antidepressant experiences.

Method

Primary research and data-collection was conducted in June-August of 2013. All ethical approvals were sought and secured through the appropriate institutional channels[1]. An internet-based self-report questionnaire "combined measure of antidepressant side effects" was developed for participant completion. Scales drew on the most prevalent side effects highlighted in existing analysis literatures and utilised the most recent, and reliable short-form measures evidenced in existing studies of medication adherence. Six short-form scales were used to measure side effects of increased depression, anxiety, sexual dysfunction, sleepiness, weight change, suicidal ideation. A measure of medication compliance was also included, and participants were asked to record any additional medications or therapy received alongside their primary antidepressant. Finally, participants were asked to record their subjective attitudes towards any side effects experienced.

Participants

The target group was any individual, taking antidepressant medication, over the age of eighteen who was not currently being treated for alcohol dependence, drug dependence or as a psychiatric inpatient - factors which may influence antidepressant effectiveness, adherence and tolerability (Stahl, 2011). A total of 517 participants began the survey (117 males, 231 females, 168 not specified). However, 172 did not fully complete the survey and these results were discarded. Of the 345 remaining completed surveys 116 (34%) participants were male (Mean: 28.30, SD+/- 8.07) and 228 (66%) were female (Mean: 26.51, SD+/- 7.49). Overall mean age of the sample was 27.11 years (SD+/- 7.71).

Side effect Measures

Depression – Beck Depression Inventory (BDI)

Depression was measured using the *Beck Depression Inventory (BDI-1A),* a 21-item self-report inventory validated for measuring depression severity in healthy populations (Beck, Steer, Garbin, 1988). The Beck Depression Inventory was selected for ease of participant completion as a short, self-administered, and reliable depression measure. The BDI holds long-standing use as a depression diagnostic tool which can be easily adapted to self-administer. It is frequently used in depression research (Faro & Pereria, 2020). Scoring ranges from a minimum of 0 to a maximum of 63. Scores over 15 indicate depression. The inventory comprised of depression symptom items including: sadness, failure, guilt and disappointment as well as measures of physical changes such as weight and fatigue. Items were scored using 4-point Likert scales (e.g. I can sleep as well as usual; I don't sleep as well as usual; I wake-up 1-2 hours earlier than usual and find it hard to get back to sleep; I wake-up several hours earlier than I used to and cannot get back to sleep). Higher overall scores indicated greater levels of depression (1-10: These ups and downs are considered normal; 11-16: Mild mood disturbance; 17-20: Borderline clinical depression; 21-30: Moderate depression; 31-40: Severe depression; Over 40: Extreme depression). Validity of the BDI is well established in literature with samples from different populations. The BDI showed adequate reliability estimates scoring a coefficient

[1] Ethical approval was secured at the institution where primary data collection was conducted.

alpha of 0.81 for non-psychiatric subjects, with a Cronbach's alpha value greater than .70 indicating reliability.

Anxiety – Beck Anxiety Inventory (BAI)

The *Beck Anxiety Inventory (BAI)* (Beck, et al. 1988) was used to measure anxiety. The BAI had twenty-one questions. Scoring ranged from a minimum score of 0 to a maximum score of 63. Responses were chosen from a 4-point Likert scale presented as a grid matrix (e.g. Not at all; mildly – but it did not bother me much; moderately – it was not pleasant at times; severely – it bothered me a lot). Questions explored physical and psychological symptoms of anxiety such as: heart pounding/racing, numbness or tingling, inability to relax, fear of dying. Higher scores indicated higher anxiety (A total of between 0-21 was indicative of very low anxiety, a grand sum of 22-35 indicated moderate anxiety, and a total exceeding 36 showed cause for concern, indicating persistently high anxiety). The BDI showed reliability and consistency when measuring anxiety, with a coefficient alpha of .94 in normal populations. A coefficient alpha greater than .70 indicated reliability (Clark et al. 2016).

Sexual Dysfunction – The PRSexDQ-SALSEX scale

The *Psychotropic-Related Sexual Dysfunction Questionnaire* (PRSexDQ-SALSEX) (Montejo & Rico-Villabemoro, 2008) was used to measure sexual side effects. The scale scored participants on DSM-IV measures of SD using six-question scales. Scores ranged from a minimum total score of 0 and a maximum total score of 15, with each of the 5 questions scoring between 0-3. Total scores of 0-5 indicated of mild sexual dysfunction, scores of 5-10 showed moderate sexual dysfunction and scores of 10-15 indicated severe SD. Scale questions were preceded with a single polar choice question (Yes/No). For example: "Have you observed any decrease in your desire for sexual activity or interest in sex?" (No problem, mild decrease; somewhat less interest, moderate decrease; much less interest, severe decrease; almost none or no interest). The PRSexDQ-SALSEX had evidenced reliability with a coefficient of .70 for individuals treated with psychiatric medications. Coefficients of .70 or greater indicated reliability. The PRSexDQ-SALSEX scale (Montejo & Rico-Villabemoro, 2008) was selected due to scoring markers highlighting specific changes in sexual function, shown to be the most reliable predictor of SD as an antidepressant side effect. Wording was viewed as more clinical, and impersonal than alternative scales considered, while remaining short and easy to complete. Such factors minimise participant embarrassment, encouraging honest responses in an area notoriously difficult to measure accurately.

Sleepiness – Epworth Sleepiness Scale

Sleepiness was measured using the *Epworth Sleepiness Scale* (Johns, 1991). A four-point Likert scale allowed participants to rate likelihood of "dozing off" in different situations. The scale contained eight questions with a minimum score of 0 and a maximum score of 24 possible. Participants scored each of the eight questions from 0-4 on a numerical scale depicting likelihood of dozing: No chance, slight chance, moderate chance, and high chance. Items (e.g. "sitting and reading") measured fatigue levels per time of day and activity. Higher scores indicated higher levels of daytime fatigue and sleepiness. In general populations, Johns, (1991) reported a coefficient alpha of .82, coefficients of .70 or greater indicating reliability.

Weight change - Short Measure Weight Change (A-SMWC)

A specific Short Measure Weight Change (A-SMWC) scale was developed purposely for this study as a short, reliable, self-completed measure of weight-change, specific to individuals taking psychiatric medications. Previous scales were long and non-specific (See Burke, Wang, Sevick, 2011). A-SMWC items were based on studying existing, longer scales of weight and appetite change. Questions were tailored to be short, concise, and narrowly descriptive while remaining rational indicators of weight changes in individuals taking antidepressants. At establishment of theoretical context, the scale item pool initially had fourteen items. Scale items were removed to increase internal consistency during inter-scale reliability analysis. The scale was reduced to six items and tested on a heterogeneous sample representing the target population as an initial pilot survey. Test-retest reliability remained high when six-item questions were randomised over three pilot studies. Scale internal consistency and inter-reliability within an initial ten-person sample showed a Cronbach's alpha of .73, a second larger sample showed a Cronbach's alphas of .71, Cronbach's alpha of .70 or greater indicating scale reliability.

The Short Measure of Weight Change (A-SMWC) asked participants to self-rate subjective experience of weight and appetite change across six questions using a 5-point Likert scale. Scores ranged between a minimum of 0 and a maximum of 24. Questions related to current perceptions of weight loss/gain and appetite increase/decrease, that is, "my current medication increases my enjoyment of food, causing me to eat more", "my current medication makes me feel so nauseous that I find myself eating a good deal less". Question four was a single measure of severity: "there are times where the weight change side effects of my medication make me want to stop taking it, despite my knowledge that the medication has been prescribed to treat symptoms of depression/anxiety". Question 1 was an initial marker of weight change: "my current medication does not affect my weight". Higher scores indicated greater incidence of weight change. The direction of weight change can be further calculated by measuring scores on questions two and six (where higher scores indicated weight gain) and questions three and five (where high score indicated weight loss). On reverse-scoring questions three and five, higher total scores indicate weight gain, low scores indicate weight loss. A-SMWC scored a Cronbach's alpha of .71 with an alpha of .70 indicating acceptable reliability.

Suicidal Ideation – Kessler Psychological Distress Scale (K10)

SI was measured using the *Kessler Psychological Distress Scale (K10)* (For a comprehensive overview see Tanhaye, 2020). The K10 consisted of ten questions with a possible minimum score of 0 and a maximum score of 40, higher scores indicating greater SI. Choices were rated on a 5-point Likert scale (e.g. none of the time, a little of the time, some of the time, most of the time, all of the time). Questions measured frequency of negative physical and mental symptoms of distress (e.g. How often did you feel tired out for no good reason? How often did you feel nervous? About how often did you feel so restless you could not sit still? About how often did you feel worthless?). Scoring of 0-15 (Group 1) indicated remote chance of a suicide attempt and a quarter of the population risk for meeting criteria of anxiety or depressive disorders; Scores between 16-21 (Group 2) indicate 1% chance (medium risk: three times the population risk) of attempting suicide and 1 in 4 chance (three times the population risk for depression disorder or anxiety disorder; Scores of 22-29 (Group 3) indicate a 6% suicide chance (high risk: twenty times the population risk) and a 3 out of 4 chance of depression and anxiety diagnosis. Scoring further decodes as: Group 1 comprise 78% of the population, their score is low: It is likely they do not require medical help. Group 2 comprise 20% of the

population: Discretion is suggested, individuals may require medical help. Group 3 comprise of 2% of the population: They require immediate medical help (Tanhaye, et al. 2020). The K10 is a reliable indicator of suicidal ideation (95%). A coefficient alpha of .91 indicated high reliability, with an alpha of .70 or greater indicating reliability.

Medication Adherence

Medication adherence was measured using the *Medication Adherence Rating Scale (MARS)* (See Thompson, Kulkarni, Sergejew, 2000), a short 10-question scale. All MARS ten questions presented as an exclusive disjunction with only a polar choice (Yes / No). Questions 2, 6, 9 and 10 were worded negatively (e.g. Are you careless at times about taking your medication; Medication makes me feel tired and sluggish?) with the remainder of questions worded positively (e.g. My thoughts are clearer on medication?). Negative questions were reverse scored. "No" scores on questions 1-6 and "yes" Scores on items 7-8 indicate compliance. Scoring was re-coded numerically in accordance with established guidance for use. A minimum total score of 10 and a maximum score of 20 was possible. 10-14 indicated poor medication compliance, 14-18 indicated moderate medication compliance, 18-20 indicated excellent medication compliance. The MARS showed a coefficient alpha of .75 in a sample of individuals taking psychiatric medications, with .70 or greater indicating reliability.

Side effects overall contribution to depression

A final question asked: "I feel the side effects caused by my medication significantly contributes to my overall feelings of depression". Responses were measured on a five-point Likert scale (Totally agree, somewhat agree, neither agree nor disagree, somewhat agree, totally disagree), the minimum total score possible was 0 and the maximum score 5. Higher scores indicated medication side effects had lower contributions to depressive feelings, while lower scores indicated side effects had greater influence on overall depression.

Procedure

A web-link to the questionnaire portal was posted on a popular social networking site, after obtaining permission from the social media organisation to share the link. The questionnaire remained online for approximately three weeks. Following this, all data was downloaded and analysed.

Analysis

Mean differences in side effects and medication adherence between participants taking SSRI vs. atypical antidepressants was examined using independent samples t-tests. Mean differences between individual antidepressant side effects were compared using one-way ANOVA. Where effect reached significance at the 5% ($p = <0.05$) level, F or t ratios and significance levels are recorded. A further Post-Hoc analysis was carried out using Fisher LSD at the 5% significance level. Chi square tests were used to compare mean differences in side effects for individuals taking SSRI vs. atypical who were taking adjunctive medication, adjunctive therapy and both adjunctive medication and adjunctive therapy. All data were analysed using SPSS.

Results

Overview Statistics

A total of 517 participants began the survey, however incomplete data was excluded leaving 345 complete responses. A further six participants were excluded due to recording multiple

contraindicated primary medications, leaving a total of 339 participants. *Table 1* illustrates the breakdown of the total sample per medication class, gender, and age.

Table 1: Breakdown of participants according to antidepressant class, gender and age.

Total Number of participants taking SSRI medications.	%age of total sample (339)	Number of Male SSRI participants	Male %age of SSRI sample	Number of Female SSRI participants	Female %age of SSRI sample	SSRI participants mean age (years)
220	64.90%	76	34.55%	144	65.45%	26.81 (SD+/- 7.68)
Total Number of participants taking atypical medications.	**%age of total sample (339)**	**Number of Male atypical participants**	**Male %age of atypical sample**	**Number of Female atypical participants**	**%age of Female atypical sample**	**Atypical participants mean age (years)**
119	35.10%	34	28.57%	85	71.43%	27.53 (SD+/- 7.82)

Five participants (three from the SSRI class, two from atypical class) listed gender as "not specified". The mean age of the total sample (345 individuals) was 27.11 years (SD+/- 7.71). An independent samples t-test showed age difference between self-identified groups was not significant: $t(337) = .86$, $p = .60$, $d = .10$.

Time on current primary medication was compared between SSRI and atypical classes. 339 participants completed the question (SSRI: 220, atypical: 119). *Table 2* illustrates responses for time taking current antidepressant medication per class.

Table 2: Time taking current antidepressant medication according to class.

Time taking current antidepressant	Less than 6 months	6 months to 1 year	2-3 years	4-5 years	Longer than 5 years	Total no. of participants
SSRI	79	74	33	16	18	220
atypical	31	46	28	11	3	119

Note: Numbers reflect participants belonging to this category.

A Chi-Square test showed time taking antidepressants did not differ significantly between SSRI and atypical groups: $\chi^2 = 10.45$. df = 5, p = 0.63.

Individuals were also asked to rate effectiveness of their primary, current antidepressant: "how good do you feel your current antidepressant is overall at treating your depression?" 339 individuals completed the question (SSRI: 220, atypical 119). In both classes, mean scores indicated overall effectiveness was rated as "good".

Table 3: Shows the breakdown of participant responses and mean scores per category and class.

Table 3: Participant effectiveness rating of current medication according to class.

Participant rating for effectiveness of current antidepressant	Very Good	Good	Barely Acceptable	Poor	Very Poor	Total no. of participants	Total Mean Score
SSRI	35	113	46	17	9	220	2.34 (SD+/- .97)
atypical	21	64	23	6	5	119	2.24 (SD+/- .95)

Note: Numbers reflect participants belonging to this category.

An independent samples t-test showed the mean difference in effectiveness rating between the SSRI and atypical groups was not significant: t (337) = .76, p = .41, d = .12.

Participants were also asked how many antidepressants they had been prescribed before their current medication. 252 participants (74.34%) – 151 from the SSRI group (68.64%) and 91 from the atypical group (76.47%) – out of the 339 total sample completed the question, with 97 (28.61%) skipping the question. *Table 4* shows the breakdown of responses for number of previous antidepressants taken according to class. Total mean score reflects the number of previous antidepressants taken.

Table 4: Responses for number of previous antidepressants taken according to class.

Number of previous antidepressant medications taken	None	1	2	3	4	More than 4.	Total No. of participants	Total Mean Score
SSRI	21	48	37	18	9	18	151	2.00 (SD+/- 1.52)
atypical	3	21	31	10	8	18	91	2.82 (SD+/- 1.61)

Note: Numbers reflect participants belonging to this category.

The mean score for the SSRI class indicated participants had taken three previous medications. The atypical class mean score indicated closer to four previous antidepressants. An independent samples t-test showed the mean difference in previous medications taken between the SSRI and atypical groups was significant: t (250), p = .03, d = .52. A further independent samples t-test showed the difference between scores as significant: t (250) = 4.06, p = .04, d = .52.

To summarise: SSRI and atypical groups did not significantly differ on measures of participant *age, time on current medication or effectiveness ratings, however, the atypical group had taken a higher number of previous antidepressants.*

Side Effect Comparison According to Antidepressant Class (SSRI vs Atypical)

SSRI and atypical classes were compared for their scores on side effects measures. *Table 5* shows mean and standard deviations for SSRI and atypical drug class side effects and medication adherence.

Table 5:
Means and Standard Deviations for SSRI and atypical drug class side effects and medication adherence.

Side Effect	Medication Class	Means	*SD*	*n*
Depression	SSRI	17.58	12.76	220
	Atypical	19.11	12.69	119
Anxiety	SSRI	21.52	15.20	220
	Atypical	22.80	15.73	119
Sleepiness	SSRI	7.17	5.11	220
	Atypical	7.51	5.12	119
Weight Change	SSRI	14.50	3.84	189
	Atypical	13.90	3.42	105
Suicidal Ideation	SSRI	15.35	10.10	220
	Atypical	16.36	9.36	119
Sexual Dysfunction	SSRI	4.87	4.21	220
	Atypical	5.03	4.16	119
Medication Adherence	SSRI	15.03	1.50	194
	Atypical	15.10	1.53	109

Note: *SD* = Standard Deviation. *n* = number of participants.

Results breakdown are as follows:

Depression. On the *Beck Depression Inventory (BDI-1A)* higher scores indicated higher levels of depression. Mean scores for both SSRI (17.58, SD+/- 12.76) and atypical (19.11, SD+/- 12.69) groups indicated only mild depression was present. An independent samples t-test showed no significant difference between depression results of the two classes: $t(337) = 1.06$, $p = .29$, $d = -.12$.

Anxiety. On the *Beck Anxiety Inventory (BAI)* higher scores indicated higher levels of anxiety. Mean scores for anxiety in the SSRI group (21.52, SD+/- 15.20) was indicative of low anxiety, while mean scores in the atypical group (22.8, SD+/- 15.73) indicated moderate anxiety. However an independent t-test showed the difference between anxiety scores was not significant: $t(337) = .73$, $p = .47$, $d = .41$.

Sleepiness. On the *Epworth scale of sleepiness* higher scores indicated a higher chance of dozing off. Mean scores for sleepiness in both the SSRI group (7.17, SD+/- 5.11) and atypical group (7.51, SD+/- 5.12) indicated low incidence of sleepiness. An independent samples t-test showed the difference between the SSRI and atypical class for sleepiness was not significant: $t(337) = .58$, $p = .93$, $d = .07$.

Weight Change. On the *Short Measure of Weight Change (A-SMWC)* higher scores indicated greater incidence of weight change. Mean scores for both the SSRI (14.50, SD+/- 3.84) and atypical (13.90, SD+/- 3.42) groups both indicated low incidence of weight change, with atypical class scoring a lower incidence of weight change side effects. An independent samples t-test showed the difference between SSRI and atypical medication class was significant: $t(292) = 1.35$, $p = .05$, $d = .17$.

Suicidal Ideation. On the *Kessler Psychological Distress Scale (K10)* higher scored indicated a higher incidence and severity of suicidal ideation. Mean scores for both SSRI (15.35, SD+/- 10.10) and atypical (16.36, SD+/- 9.36) groups indicated a 1% chance of attempting suicide (three times standard population risk) classified as medium risk. While the atypical group recorded a higher incidence of suicidal ideation as a side effect, an independent samples t-test showed the difference between the two classes was not significant: $t(337) = 9.07$, $p = .20$, $d = .10$.

Sexual Dysfunction. On the *Psychotropic-Related Sexual Dysfunction Questionnaire* (PRSexDQ-SALSEX) higher scores indicated a higher incidence of sexual dysfunction. The mean score for the SSRI group was 4.87 (SD+/- 4.21) indicating mild sexual dysfunction. The mean score for the atypical group was 5.03 (SD+/- 4.16) indicating moderate sexual dysfunction. An independent samples t-test showed the difference in sexual dysfunction between the SSRI and atypical groups was not significant: $t(337) = .32$, $p = .67$, $d = .04$.

Medication Adherence. A total of 303 participants completed the education adherence question, 36 individuals skipped the question. On the *Medication Adherence Rating Scale (MARS)* higher scores indicated higher levels of medication adherence. Mean scores from both groups indicated "moderate" medication compliance: SSRI (Mean: 15.0, SD+/- 1.50) vs. atypical (Mean: 15.1, SD+/- 1.53). An independent t-test showed the difference between SSRI and atypical class for medication compliance was not significant: $t(301) = .41$, $p = .68$, $d = .05$.

The only significant reduction in side effects for atypical drugs compared with SSRIs was lower incidence of weight change. Results suggest atypical drugs may have weight change sparing compared with SSRIs. However, overall findings did not support reduced atypical side effects.

Side effect Comparison Between Newer and Older SSRI and Atypical Antidepressant Drugs

Side effect scores from six antidepressant medications from the SSRI and atypical class were compared (Citalopram, Escitalopram, Fluoxetine, Venlafaxine, Desvenlafaxine and Bupropion). Table 6 illustrates a breakdown of means and standard deviation scores for specific drugs according to side effects.

Table 6: Number of participants, Means and Standard deviation scores for specific antidepressant drugs according to side effects.

Side Effect	Antidepressant Drug and Class	Means	*SD*	*n*
Depression	Citalopram (SSRI)	16.93	13.13	46
	Escitalopram (SSRI)	16.48	12.28	52
	Fluoxetine (SSRI)	20.65	14.04	46
	Venlafaxine (atypical)	19.41	13.47	27
	Desvenlafaxine (atypical)	15.25	13.25	12
	Bupropion (atypical)	18.41	12.14	35
Anxiety	Citalopram (SSRI)	20.52	15.90	46
	Escitalopram (SSRI)	21.13	16.60	52
	Fluoxetine (SSRI)	20.67	12.83	46
	Venlafaxine (atypical)	20.48	14.34	27
	Desvenlafaxine (atypical)	20.08	15.13	12
	Bupropion (atypical)	20.49	13.77	35
Sexual Dysfunction	Citalopram (SSRI)	4.48	4.05	46
	Escitalopram (SSRI)	4.60	4.12	52
	Fluoxetine (SSRI)	5.61	4.46	46
	Venlafaxine (atypical)	5.33	4.34	27
	Desvenlafaxine (atypical)	4.83	3.64	12
	Bupropion (atypical)	4.80	4.22	35
Sleepiness	Citalopram (SSRI)	6.52	5.36	46
	Escitalopram (SSRI)	6.84	5.64	52
	Fluoxetine (SSRI)	7.70	4.14	46
	Venlafaxine (atypical)	7.26	5.90	27
	Desvenlafaxine (atypical)	9.42	6.01	12
	Bupropion (atypical)	7.40	4.05	35
Weight Change	Citalopram (SSRI)	14.69	4.22	39
	Escitalopram (SSRI)	14.68	3.88	41
	Fluoxetine (SSRI)	14.45	3.42	44
	Venlafaxine (atypical)	13.77	4.02	22
	Desvenlafaxine (atypical)	14.91	3.11	11
	Bupropion (atypical)	14.03	3.28	32
Suicidal Ideation	Citalopram (SSRI)	14.59	9.85	46
	Escitalopram (SSRI)	12.92	10.40	52
	Fluoxetine (SSRI)	18.72	9.80	46
	Venlafaxine (atypical)	14.15	8.96	27
	Desvenlafaxine (atypical)	16.08	9.85	12
	Bupropion (atypical)	16.86	8.92	35
Medication Adherence	Citalopram (SSRI)	15.00	1.52	39
	Escitalopram (SSRI)	15.27	1.32	44
	Fluoxetine (SSRI)	15.20	1.50	45
	Venlafaxine (atypical)	14.88	1.73	24
	Desvenlafaxine (atypical)	15.35	1.36	11
	Bupropion (atypical)	15.44	1.32	32

Note: *SD* = Standard Deviation. *n* = number of participants.

A one-way ANOVA was used to examine side effects of the six antidepressants. No significant differences were found between side effects for each of the six drugs: Depression – $F(5, 212) = .99$, $p = .43$; Anxiety – $F(5, 212) = .06$, $p = 1.00$; Sexual Dysfunction – $F(5, 212) = .47$, $p = .80$; Sleepiness – $F(5, 212) = .76$, $p = .58$; Weight Change – $F(5, 183) = .32$, $p = .90$; Suicidal

Ideation – $F(5, 212) = 2.07$, p = .07. Further, no differences were found in medication adherence: MARS – $F(5, 189) = .60$, p = .70. When suicidal ideation was shown to approach significance further analysis was carried out. Post-hoc comparison using Fisher LSD illustrated SI differences at the .05 level of significance for Fluoxetine when compared with Citalopram ($p = .04$) and Escitalopram ($p = .00$) but not for Venlafaxine ($p = .60$), Desvenlafaxine ($p = .31$) or Bupropion ($p = .65$). Results suggested atypical drugs did not have reduced SD as a side effect. Results showed no significant benefits of reduced side effects from any of the six antidepressants over another, despite some being new and some old. Surprisingly, post-hoc tests suggested atypical drugs had increased SI compared to some SSRIs.

Comparison of Participants Receiving Adjunct Medications and Therapy

Within both drug classes (SSRI and atypical) there were individuals taking adjunctive medications. Table 7 shows a total and percentage summary of individuals taking adjunctive medications by name of adjunctive drug and primary medication class.

Table 7:
Total and percentage summary of individuals taking adjunctive medications by adjunct drug and primary medication class.

Adjunct medication name	Number of SSRI group participants taking medication	% of total SSRI group taking adjunct medication	Number of atypical group participants taking medication	% of total atypical group taking adjunct medication
Mood Stabilizer	10	4.55%	9	7.56%
Buspirone	3	1.36%	5	4.20%
Mirtazapine	0	0%	1	0%
Bupropion	4	1.82%	4	3.36%
Benzodiazepine	28	12.73%	14	11.76%
Antipsychotic	7	3.18%	1	0.84%
Multiple Adjunct	8	3.64%	12	10.08%
Agomelatine	0	0%	1	0.84%
Total	60	27.27%	47	39.50%

Note: The category 'Multiple Adjunct' referred to individuals taking more than 1 adjunctive medication, for example: Mirtazapine and Benzodiazepine.

A greater percentage of individuals within the atypical class **(nearly 40%)** were taking medication to supplement their primary drug compared to the SSRI class (27%). A Chi-Square test showed the difference as significant: $\chi^2 = 17.35$, df = 8, $p = .03$. Results showed the atypical antidepressants were more strongly associated with adjunct medications. Within both groups a Benzodiazepine adjunct was the most common. Of note is that a higher percentage of multiple adjuncts medications were seen in the atypical group compared to SSRI.

Within both drug classes there were individuals receiving adjunctive therapy alongside antidepressants. Table 8 shows total and percentage summary of individuals receiving adjunctive therapy by adjunctive therapy type and primary medication class.

Table 8:
Total and percentage summary of individuals receiving adjunctive therapy by type of adjunct therapy and primary medication class.

Type of adjunct therapy	Number of SSRI group participants receiving therapy	% of total SSRI group receiving therapy	Number of atypical group participants receiving therapy	% of total atypical group receiving therapy
CBT	72	32.73%	36	30.25%
Light Therapy	3	1.36%	2	1.68%
Dialectical Behaviour Therapy	1	0.45%	2	1.68%
Talk Therapy of Counselling	6	2.73%	5	4.20%
Psychotherapy	0	0%	5	4.20%
Multiple Adjunct	7	3.18%	4	3.36%
Total	89	40.45%	54	45.38%

Note: The category 'Multiple Adjunct' referred to individuals participating in more than 1 adjunctive therapy, for example: CBT and Light Therapy.

The percentage of individuals receiving adjunct therapy was greater in the atypical class (45.38%) compared with the SSRI class (40.45%). A Chi-Square test showed the difference as not significant: $\chi^2 = 11.61$, df = 6, $p = .07$, the result however, approaching significance.

CBT was the most popular adjunct therapy within both groups. Results suggested requirements for adjunct therapy were comparable in SSRI and atypical antidepressants.

Several participants (n=55) were taking both adjunct medication and receiving adjunct therapy. *Table 9* illustrates a summary of individuals taking both adjunctive medications and adjunctive therapy according to medication/therapy combination and primary medication class.

Table 9:
Summary of individuals taking both adjunctive medications and adjunctive therapy summarised by medication/therapy combination and primary medication class.

Description of Adjunct medication and therapy.	Number of SSRI group participants undergoing adjunct therapy and taking adjunct medication	% of total SSRI group participants undergoing adjunct therapy and taking adjunct medication	Number of atypical group participants undergoing adjunct therapy and taking adjunct medication	% of total atypical group participants undergoing adjunct therapy and taking adjunct medication
Benzodiazepine + Psychotherapy	1	0.45%	1	0.84%
Buspirone + CBT	2	0.91%	2	1.68%
Mirtazapine + CBT	0	0%	2	1.68%
Wellbutrin + CBT	3	1.36%	0	0%
Benzodiazepine + CBT	12	5.45%	5	4.20%
Benzodiazepine & Mood Stabiliser + CBT & Light Therapy	1	0.45%	2	1.68%
CBT + Mood Stabiliser	5	2.27%	2	1.68%
Agomelatine + Psychotherapy	0	0%	1	0.84%
Benzodiazepine + DBT, CBT & Psychotherapy	3	1.36%	1	0.84%
Benzodiazepine & Mood Stabiliser + CBT	1	0.45%	4	3.36%
Benzodiazepine + Light Therapy	1	0.45%	1	0.84%
Benzodiazepine & Buspirone + Light Therapy	0	0%	1	0.84%
Benzodiazepine + Talk Therapy/Counselling	1	0.45%	0	0%

Wellbutrin + Talk Therapy/Counselling	0	0%	1	0.84%
Benzodiazepine & Stimulant (Adderall) + CBT	0	0%	1	0.84%
Buspirone + DBT	1	0.45%	0	0%
Total	31	14.09%	24	20.17%

Note: CBT = Cognitive Behavioural Therapy. DBT = Dialectical Behavioural Therapy.

Results varied in terms of primary and secondary medication and therapies combinations. Combined CBT and Benzodiazepine therapy was the most common adjunct in both SSRI and atypical groups. A higher percentage of individuals within the atypical group (20.17%) were receiving both adjunct medication and adjunct therapy compared to the SSRI group (14.09%). A Chi Square test showed the difference as not significant: $\chi^2 = 17.70$, df = 15, $p = .28$. Findings suggest atypical drugs do not have reduced requirements for combined adjunctive medications and therapy compared to SSRIs.

Antidepressant Side Effects Overall Contribution to Depression

A final question asked individuals to rate the extent participants felt side effects of current antidepressant medication contributed to overall feelings of depression. 290 individuals completed the question from the total sample of 339 (85.55%): 185 from the SSRI group (84.09%) (Mean: 2.83, SD +/- 1.24) and 105 from the atypical group (88.24%) (Mean: 2.63, SD +/- 1.29), with 49 participants (14.45%) skipping the question. Mean scores from both the SSRI and atypical groups indicated participants neither agreed nor disagreed with the statement. Results are summarised below in Table 10 by question choice and medication class.

Table 10:
Summary of responses for 'I feel the side effects caused by my medication significantly contributes to my overall feelings of depression'.

Question: I feel the side effects caused by my medication significantly contribute to my overall feelings of depression	Number of SSRI group participants responses	Number of atypical group participants responses
Totally agree	7	8
Somewhat agree	28	15
Neither agree nor disagree	33	20
Somewhat disagree	38	27
Totally disagree	79	35
Total	185	105

An independent samples t-tests showed no significant differences in ratings between the SSRI and atypical groups: $t(288)$, $p = .61$, $d = .16$. Results may suggest side effects which contribute to depression are not sufficiently reduced in atypical medications compared to SSRIs, with both groups reporting neutral responses. Results may be reflective of previous measures highlighting only weight change as a benefit for atypical antidepressants.

Discussion

This section breaks down the key findings of this research as related to side effect differences between newer and older antidepressant medications.

Depression

No differences were found in side effects of depression when comparing SSRI and atypical medication groups. Both SSRI and atypical medications groups reported only "mild" depression. A possible explanation may be that most participants had taken medication for over 6 months, allowing for side effect adjustment. However, participants rated an average of "neither agree nor disagree" on a measure of side effects contribution to depression, suggesting side effects were still bothersome. Adjunctive medications and adjunctive therapies which may reduce side effects were also common in both groups. Results failed to suggest atypical antidepressants carry reduced depression side effects vs SSRI medications.

Anxiety

For anxiety side effects, results showed no significant differences between SSRI and atypical classes, despite the SSRI class scoring anxiety as "low" and the atypical class "moderate". Findings suggested atypical agents did not possess reduced anxiety side effects from SSRIs. Results may be reflective of participants from both groups having high adjunct medication rates, most which were anti-anxiety treatments (benzodiazepines).

Sexual Dysfunction

Results indicated no difference in sexual dysfunction side effects between SSRI and atypical classes, with "mild" SD present in the SSRI group and "moderate" SD in the atypical group. A possible explanation is that only 5.88% of the atypical sample was taking the atypical medication Mirtazapine and 0% Moclobermide; antidepressants suggested as having the least SD (Montejo & Rico-Villademoros, 2008). However, Foley, DeSanty & Kast (2006) found the atypical Bupropion improved sexual function. As 29.41% of the atypical sample was taking Bupropion, the absence of SD sparing results is unexpected. Notably, high numbers of both SSRI and atypical groups were taking adjunctive medications which actively minimise SD side effects. Also, of note is that within the SSRI group, 21.82% of participants were taking Citalopram, 22.73% Fluoxetine and Paroxetine 8.18%; antidepressants shown to be high in SD (Montejo et al. 2001). Montejo et al. (2001) found the atypical drug Venlafaxine had a higher incidence of SD compared with same-class drugs, and even some SSRIs (Sertraline, Fluvoxamine). As 22.69% of the atypical sample were taking Venlafaxine, this may have influenced atypical results. Results failed to demonstrate SD sparing for atypical antidepressants, despite high numbers of the SSRI group taking medications most strongly associated with SD. Findings suggest atypical drugs by default may not carry reduced SD effects over SSRIs.

Sleepiness

No significant differences were found between SSRI and atypical groups, both reporting low sleepiness side effects.

Weight Change

Weight change was the only significant factor to differ between SSRI, and atypical class medication groups. While both groups reported low incidence of weight changes, atypical drugs showed significantly less change compared to SSRIs. This was unexpected, as the atypical drug Mirtazapine is well-evidenced as an appetite stimulant (Stahl, 2011), and the atypical Bupropion shown to be an appetite suppressor (Stahl, 2011). SSRIs were shown to be relatively weight neutral by comparison, with Paroxetine the exception (Stahl, 2011). However, only 8.18% of the SSRI sample was taking Paroxetine. Results may be due to the atypical sample having a low number of participants taking weight-gain associated medications such as Mirtazapine (5.88%), but a relatively high number taking weight-loss associated medications such as Bupropion (29.41%). Kivimäki et al. (2010) discuss how weight loss in antidepressant therapy is commonly framed positively by patients and discussed as a desirable side effect. Serretti & Mandelli (2010) suggest individuals prefer to attribute weight loss to personal effort as opposed to medication effects, highlighting potential self-report anomalies within the atypical sample. A further possibility is that the SMWC scale, which was purposely developed for this study may have influenced findings. While the scale evidenced satisfactory reliability in several small samples, reliability may be increased by further clinical and empirical testing, particularly within additional large real-world samples.

Suicidal Ideation

Findings showed no significant differences between the SSRI and atypical classes for SI, with both showing medium risk.

Summary

In summary, side effect comparison of atypical vs. SSRI class found reduced incidence of weight change as the only reduced side effect benefit of atypical medications. Characteristics of the sample and scale measures may not be discounted as influencing factors.

Medication Adherence

Some studies suggest atypical-class antidepressants have greater medication adherence compared with SSRIs due to their predicted reduced side effect profiles. Results found medication adherence did not significantly differ between atypical and SSRI classes. Neither group scored higher than "moderate" medication adherence, suggesting over 300 participants had difficulty adhering to their antidepressant. Explanations for results may be related to novel study design – with most participants taking current medication for at least 6 months – as well as having taken at least two previous medications. This may have allowed participants to find their "comfort level" through trial-and-error antidepressant switching, while adjusting to side effects and finding compatible adjunct treatments. While overall antidepressant effectiveness was rated as "good", adjunctive treatment and therapy was common in both classes. As depression was found to be "mild", the purpose of additional treatments may have been to counter side effects of primary medication, for example "moderate" anxiety in the atypical group. This is further supported by both groups' neutral rating of medication side effects contribution to depression with the response of "neither agree nor disagree", as well as SI scores for both groups indicating "medium" suicide risk.

Newer Antidepressant Drugs Within Both Classes

It may be expected that within both SSRI and atypical classes, newer antidepressant drugs have reduced side effect profiles compared with older antidepressants. Some studies highlight Bupropion, Venlafaxine and Escitalopram as particularly side effect sparing (See Cipriani et al. 2009; Sanchez et al. 2003). However, side effect comparison of Citalopram (old-SSRI; 1989), Escitalopram (new-SSRI; 2003), Fluoxetine (old-SSRI; 1987), Venlafaxine (old-atypical; 1993), Desvenlafaxine (new-atypical; 2007) and Bupropion (new-atypical; 2000) did not support this, with no significant differences in side effects of depression, anxiety, sexual dysfunction, sleepiness, weight change, suicidal ideation or medication adherence found.

Some studies (Cipriani et al. 2009; Einarson, 2004) have claimed Escitalopram (2003) presents reduced anxiety/stimulation and insomnia compared with Citalopram (1989). However, in direct comparison of old vs new same-class agents, Escitalopram vs Citalopram showed no significant differences on scores of anxiety and sleepiness. Similarly, Desvenlafaxine (2007) has been upheld as carrying reduced weight change and anxiety over Venlafaxine (1993) (Reddy et al. 2010). However, no side effect differences were found. Others have asserted that Bupropion (2000) has reduced side effects of weight gain, daytime sleepiness, and SD (Foley, DeSanty & Kast, 2006). However, Weight change, sleepiness and SD scores for Bupropion did not differ from that of other antidepressants.

While suicidal ideation did not differ significantly between medications, scores approached significance. The older SSRI Fluoxetine (1987) rated highest for suicidal ideation. Fluoxetine was followed by the atypical Bupropion (2000), atypical Desvenlafaxine, Citalopram (1989), Venlafaxine (1993) then Escitalopram (2003). Post-hoc analysis of SI scores illustrated significant differences for Fluoxetine against the two other SSRIs, but not the three atypical drugs. Findings position that atypical drugs do not have decreased SI, tentatively suggesting some atypical agents may increase SI risk compared with some SSRIs.

Overall results may be reflective of the sample, SI was previously shown as medium within both atypical and SSRIs, while other side effects were low (except for "moderate" anxiety in the atypical sample). Effects of adjunctive medication and therapy may have influenced tolerability reporting across all six antidepressants. For example, participants taking Escitalopram with the adjunctive anxiolytic medication Buspirone may rate anxiety as lower than participants taking Escitalopram with Mirtazapine, due to the anxiolytic effect of Buspirone (See Stahl, 2011). While several individuals were taking only primary medication, most participants were receiving adjunctive therapy, medication or both; with medication adherence also not significantly different between SSRI and atypical antidepressant classes.

Adjunctive Treatments

It could be expected participants taking the older class of medications (SSRI) would have a greater need for treatment with adjunctive medications, adjunctive therapies, or both. Studies suggest adjunctive medications are primarily utilised to manage side effects from SSRI drugs (See Atmaka et al. 2011). Other scholars suggest reduced side effects of atypical antidepressants may minimise requirements for adjunctive treatments (See Wade et al. 2011). Surprisingly, results found a significantly higher percentage of the atypical sample were taking adjunct medication compared with the SSRI group.

A benzodiazepine adjunct (an anxiolytic) was the most popular in both groups. Anxiety scores of "moderate" for the atypical group and "mild" for SSRIs may suggest anxiety as either a comorbid condition or a side effect of medications. Further, low sleepiness scores for both classes may highlight on-going sleep problems. Fava et al. (2006) has discussed sleepiness as a SSRI side effect which does not resolve in long-term treatment. Benzodiazepine therapy is common in initial antidepressant treatment to minimise "start-up" effects of anxiety and insomnia (Stahl, 2011), however participants had largely been taking primary medication for over 6 months, possibly highlighting on-going side effects in both classes.

Findings may be for several reasons. Participants taking atypical medication may have more severe depression that the SSRI group, suggesting a higher need for adjuncts. While depression ratings were "mild", this may only reflect relative success of current medication regime, not baseline diagnosis. Members of the atypical group may also have previously taken SSRI medication, finding inadequate efficacy or tolerability; this thinking is supported by the atypical group having a significantly higher total of previous antidepressant medications compared with the SSRI group. NICE (Clark, 2011) guidelines dictating first treatment with an SSRI followed by an atypical drug further support this. NICE also asserts adjunctive medication may be combined with atypical drugs in cases of treatment resistant depression (Middleton et al. 2005).

Comparison of SSRI vs. atypical participants receiving adjunct therapy showed no differences between groups; however, differences approached significance, with a greater percentage of atypical participants receiving adjunct therapy. Of note is that over a third of both samples were receiving CBT, where other therapy totals did not exceed 5%. Some evidence suggests adjunctive CBT is associated more strongly with SSRIs (See Semple & Smyth, 2013; Stahl, 2011). However, findings failed to support this, indicating atypical antidepressants did not have reduced adjunctive therapy requirements. Of note is that results approached significance, with higher rates of adjunct therapy in atypical participants. By explanation, members of the atypical group may have initially been receiving combination SSRI and therapy treatment, choosing to continue therapy when switching to an atypical antidepressant. The atypical group rating "moderate" and the SSRI group "low" for anxiety is also a possible consideration.

When individuals receiving both adjunct medication and therapy were compared by class no differences were found. Results indicated atypical antidepressants did not have reduced incidences of combined adjunct medication and therapy. Findings may indicate that primary medication side effects are on-going, requiring additional treatments; however, factors such as anxiety and sleeplessness could equally be characteristic of individual illness presentation. Results failed to support notions that participants taking older SSRI-class antidepressants have a de facto greater need for treatment with adjunctive medications, adjunctive therapies, or both.

Limitations

A general point regarding use of self-report measures is that participant bias is difficult to control for. Efforts were made to mitigate bias by including reverse-scoring within scales (A-SMWC, BDI, and BAI). However, participant bias may be an inherent presence for self-report measures that can influence inflated (or reduced) reporting of side effects. A notable observation is that within both medication classes, adherence was found to be "moderate". This may have influenced side effect reporting, with perfect medication compliance frequently highlighted as key to achieving antidepressant tolerability and efficacy (Stahl, 2011). The data for this study is also historic, gathered in 2013. However, despite any limitations, this study presents interesting findings that are important to document in the immediate 2020 climate of interest surrounding real world sampling studies. Research contributes to a recently emerging body of literature examining antidepressant tolerability and side effect comparison in random samples independent from clinical trials.

Conclusion

This study concludes that, in a comparison of +300 individuals taking a variety of different antidepressant mediations – for atypical vs. SSRI antidepressant side effects, the only clear reduced side effect of atypical antidepressants compared with SSRIs was a lack of weight change. No atypical drug benefits were found for side effects of depression, anxiety, sleepiness, suicidal ideation, sexual dysfunction, and medication adherence over SSRIs. On comparing side effects of six new and old atypical and SSRI antidepressants, no reduced side effects or medication adherence was found for newer drugs. In examining adjunctive medications and therapy, atypical antidepressants were linked to greater need for adjunct medication, a finding which may be surprising, and resists some claims of superior tolerability. Adjunct therapy rates were found not to differ significantly from atypical and SSRI groups, although this approached significance for increased atypical adjuncts, suggesting a lack of atypical superiority and possible shortcomings of ongoing atypical treatment. Measures of combined adjunct medication and therapy found no significant differences between atypical and SSRI groups. While weight change side effects were found to be improved for newer medications, it was discussed how this may be reflective of scoring measures used. Aside from weight change, this study concluded no benefits of reduced side effects could be found for newer antidepressants when examining a random sample of individuals taking a variety of common antidepressant medications. This study provides evidence to support arguments that the reduced side effects and improved tolerability often claimed as characteristic of newer antidepressants may be overstated when exploring non-clinical "random" samples (Healy, 2018). As many emerging studies now uphold, examinations of "real-world data" provides a valuable avenue of exploration to clarify how drug side effects manifest and present in everyday life, as opposed to the controlled environments of clinical trial settings. The "real world" is, after all, the natural environment within which most humans taking antidepressants exist day-to-day.

Note of Interest

The research paper documents primary data from a study conducted for my past MSc dissertation at Brunel University London (2013). Primary research was conducted, and data collected for this research purpose.

Declarations

No funding was received, or conflict of interest exists for this research.

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