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REVIEW ARTICLE

Glucose dysregulation associated with antidepressant agents: an analysis of 17 published case reports

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Abstract *Aim of the review* Although there are several case reports in literature linking use of antidepressants and disturbances in glucose control, it is difficult to identify risk factors for serious adverse drug events from individual case reports. The aim of this review is to provide a descriptive analysis of the demographic and clinical characteristics of published glucose dysregulation case reports following initiation of antidepressant agents. *Methods* Published case reports of glucose dysregulation associated with antidepressants were accessed through PubMed (Medline), PsycINFO, and Web of Science (WOS) between January 1, 1970 and April 30, 2010. The following key words were used: antidepressant agents, glucose dysregulation, hypoglycemia, hyperglycemia, diabetes mellitus, and diabetic ketoacidosis. Case reports were excluded if glucose dysregulation occurred after a drug overdose/improper dosing or after the patient was prescribed drugs known to cause glucose disturbances in addition to antidepressant agents. *Results* Out of the 17 cases reports reviewed, nine (53%) were of hyperglycemia while eight (47%) were of hypoglycemia. Hyperglycemia was reported following treatment with clomipramine, fluvoxamine, imipramine, mianserin, mirtazapine, paroxetine, and sertraline. Hypoglycemia was reported following treatment with doxepine, fluoxetine, imipramine, nefazodone, nortriptyline, maprotiline, and sertraline. Fourteen out of the seventeen patients were female (82%) while ten had a history of diabetes mellitus (59%). The average age of the patients was 53.9 (SD = 17.5) years (range: 24–84 years). The time to onset of glucose dysregulation ranged from 4 days to 5 months after initiation of antidepressant therapy. More than two-thirds (68%) of the cases (n = 11) reported glucose control disturbances within 1 month of therapy. *Conclusions* It is not clear from published case reports whether changes in glucose regulation, following antidepressant therapy initiation are due to antidepressants or changes in mood and lifestyle. Nonetheless, healthcare providers should be aware of the potential changes in glucose regulation especially in the first month of antidepressant therapy, and use appropriate clinical and laboratory monitoring to prevent serious adverse events in patients at risk.

Keywords Antidepressant agents · Case reports · Glucose dysregulation

Impacts on practice

- It is not clear whether glucose dysregulation following antidepressant therapy is related solely to antidepressants and not patient clinical characteristics.
- Changes in glucose regulation following antidepressant therapy may be related to changes in mood and lifestyle.
- Changes in glucose regulation are more likely to occur within 1 month of starting antidepressant therapy.

Introduction

Recent evidence from observational studies suggests that long-term use of antidepressants increases the risk of developing diabetes [1–4]. However, results from these studies are equivocal. While two studies showed that antidepressant use is associated with a significant increase

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in the risk of diabetes [1, 4], two other studies did not find an association between diabetes and antidepressants [2, 3]. Furthermore, the evidence from randomized controlled trials (RCTs) has also been equivocal. While two RCTs observed an increase in the risk for diabetes associated with use of antidepressant agents [5, 6], use of antidepressants in another RCT was observed to cause a decrease in fasting plasma glucose [7].

In contrast to the studies linking antidepressants use and increased risk for diabetes, recent studies report that use of antidepressants may increase the risk for hypoglycemia [8, 9]. A recent analysis of spontaneous reports in the World Health Organization (WHO) Adverse Drug Reaction Database showed that use of antidepressants increases the risk for both hyperglycemia and hypoglycemia [9]. In that study by Derijks et al., use of antidepressants was associated with a 1.5-fold increase in the risk for hyperglycemia (Reporting Odds Ratio [ROR] = 1.52; 95% CI: 1.20–1.93) and a 1.8-fold increase in the risk for hypoglycemia (ROR = 1.84; 95% CI: 1.40–2.12) [9]. Similarly, a nested case–control study showed that long-term use (>3 years) of antidepressants in patients with diabetes was associated with a 2.8-fold increase in the risk for severe hypoglycemia (OR = 2.75; 95% CI: 1.31–5.77) [8]. In both studies, hypoglycemia was most associated with antidepressants with affinity for the serotonin reuptake transporter (i.e., selective serotonin reuptake inhibitors and clomipramine) [8–10]. On the other hand, hyperglycemia was most associated with antidepressants with high binding affinity for the 5-HT_{2c} receptor (serotonin), H_1-receptor (histamine), and norepinephrine reuptake transporter (i.e., amitriptyline, doxepin, imipramine, maprotiline, nortriptyline, mianserin, mirtazapine) [8, 10] (see "Appendix").

The involvement of serotonin in glucose regulation is well established [11–13]. Drugs that are agonists at the central serotonin receptors (i.e., 5-HT_{2A} and 5-HT_{2B}) have been shown to induce hyperglycemia [12, 13]. It has also been postulated that antidepressants induce hyperglycemia through inhibition of insulin signaling cascade leading to insulin resistance [14, 15]. Another mechanism involves the hypothalamo-pituitary-adrenal (HPA) axis. Antidepressants can induce elevation of cortisol leading to insulin resistance and subsequently to hyperglycemia [16, 17]. In contrast, antidepressants may cause hypoglycemia by increasing insulin sensitivity [18–20].

Antidepressant agents have been also been associated with weight gain leading to obesity, a risk factor for diabetes mellitus [21–23]. The exact mechanism of weight gain associated with antidepressants has not been fully elucidated. However, several mechanisms have been proposed. It has been postulated that weight gain results from improved eating habits as symptoms of depression diminish following antidepressant therapy initiation [21]. This hypothesis does not, however, fully account for differences in the magnitude of weight gain associated with different antidepressant agents. Therefore, antidepressants are also thought to independently increase weight by increasing appetite and inducing a craving for carbohydrates [21, 22, 24].

Given the ambivalence in the evidence linking antidepressants with disturbances in glucose regulation, it is essential to conduct more studies that may shed light on the nature of the relationship between antidepressants and glucose control. In addition, the frequent use of antidepressants in patients with diabetes mellitus makes it important to understand the potential risk factors and the relationship between antidepressants and glucose dysregulation [25–28]. Although there are several case reports in literature linking use of antidepressants and disturbances in glucose control, it is difficult to identify risk factors for serious adverse drug events from individual case reports. An analysis of large number of adverse drug events using databases of spontaneous reports, such as the WHO Adverse Drug Reaction Database, can help identify risk factors for serious adverse drug events. In addition, an analysis of published case reports may complement evidence from the few observational studies conducted to date by providing a better understanding of unique patient characteristics that may be related to serious adverse drug events. In this regard, an analysis of the phenomenology of the glucose dysregulation case reports may provide additional insight on risk factors of glucose dysregulation following antidepressant therapy.

Aim of the review

The purpose of this review is to provide a descriptive analysis of the demographic and clinical characteristics of published case reports which may help clinicians identify high-risk patients that require intensive glucose monitoring during therapy with antidepressants.

Methods

An English language literature search using PubMed (Medline), PsycINFO, and Web of Science (WOS) was conducted to identify all single cases or series of cases published between January 1, 1970 and April 30, 2010 associating the use of antidepressant agents and glucose dysregulation. The following key words were used: antidepressant agents, glucose dysregulation, hypoglycemia, hyperglycemia, diabetes mellitus, and diabetic ketoacidosis. The electronic searches were complemented by manually searching the bibliographies of every article reporting on

the association between antidepressant agents and glucose dysregulation.

Articles were included if they were case reports of antidepressants that reported on glucose control disturbances following antidepressant therapy. In addition, only articles published in English were included in the review. Articles were excluded if they were not case reports, not published in English, and if glucose control disturbance occurred after a drug overdose or improper dosing. Furthermore, cases were excluded if glucose dysregulation was reported after the patient, in addition to antidepressants, was prescribed drugs known to cause glucose disturbances [29, 30].

For each case of glucose dysregulation associated with antidepressant therapy, data on demographic and clinical characteristics were collected. Demographic characteristics included: year of publication, country of origin, patient age, and gender. Clinical characteristics included: type of event reported (i.e., hypoglycemia, hyperglycemia or ketoacidosis), antidepressant daily dose, body mass index, patient history of diabetes, time to onset, time to glucose normalization, weight changes, and highest or lowest glucose level recorded during an episode of glucose dysregulation after antidepressant therapy initiation. An episode of glucose dysregulation was defined as the period between the first date of changes in glucose control to the date on which glucose levels were normalized or returned to baseline levels.

Results

A total of 542 potential articles were identified from electronic databases and manual searches of bibliographies. Out of these, 508 were excluded after screening the titles while 15 were excluded after reviewing the abstracts. Three of the remaining 19 articles were excluded after reading the full articles. One case report of hyperglycemia and ketoacidosis after treatment with venlafaxine was excluded because the patient was also taking olanzapine and valproic acid, both of which are linked to hyperglycemia [31]. Another case report of hypoglycemia was excluded because the patient received high doses of sertraline concurrently with glyburide and risperidone [32]. Lastly, one case report of hypoglycemia was excluded because the patient had taken an overdose of venlafaxine [33].

A total of 17 case reports published in 16 articles met the inclusion criteria and were included in this review. Table 1 provides a summary of the seventeen (n = 17) case reports that met the inclusion criteria. The reports involved 12 different antidepressant agents: clomipramine (n = 1), doxepin (n = 1), fluoxetine (n = 1), fluvoxamine (n = 1), imipramine (n = 2), nefazodone (n = 1), nortriptyline (n = 1), maprotiline (n = 2), mianserin (n = 1), mirtazapine (n = 3), paroxetine (n = 1), and sertraline (n = 2).

Although the first case report was published in 1983, the majority of the case reports were published in the past 15 years. Out of the 17 cases reports, nine (53%) were of hyperglycemia while eight (47%) were of hypoglycemia. One patient who presented with hyperglycemia also presented with diabetic ketoacidosis and pancreatitis [34]. Hyperglycemia was reported following treatment with clomipramine (n = 1) [35], fluvoxamine (n = 1) [17], imipramine (n = 1) [36], mianserin (n = 1) [37], mirtazapine (n = 3) [34, 38, 39], paroxetine (n = 1) [40], and sertraline (n = 1) [41]. Hypoglycemia was reported following treatment with doxepin (n = 1) [42], fluoxetine (n = 1) [43], imipramine (n = 1) [44], nefazodone (n = 1) [45], nortriptyline (n = 1) [42], maprotiline (n = 2) [46, 47], and sertraline (n = 1) [48]. Sertraline and imipramine were both associated with hyperglycemia and hypoglycemia [36, 41, 44, 48]. Fourteen out of the seventeen patients were female (82%). Ten patients (59%) had a history of diabetes mellitus. The average age (SD) of the patients was 53.9 (±17.5) years (range: 24–84 years). In addition, the reported body mass index ranged from 19.7 to 26.7 kg/m^2 indicating that the patients' weight ranged from normal to overweight.

The time to onset of glucose dysregulation ranged from 4 days to 5 months after initiation of antidepressant therapy. More than two-thirds (68%) of the cases (n = 11) reported glucose control disturbances within 1 month of therapy. However, most cases that occurred after more than 2 months of therapy were associated with severe effects on glucose levels which may indicate cumulative effects of antidepressant agents on glucose control [34, 35, 38, 43].

There was a temporal relationship in all the case reports between use of antidepressant agents and glucose dysregulation. In addition, blood glucose levels were normalized or returned to stable levels after the antidepressant agent was discontinued and re-challenging was associated with further deterioration of glucose regulation. In most patients, glucose levels normalized within a few days (i.e., 1–7 days) of discontinuation of antidepressant therapy. Further, a dose–response relationship was observed in some patients in whom reducing the dose of the antidepressant agent was accompanied by a corresponding improvement in glucose levels while an increase in the dose was followed by deterioration in the glucose control [36, 37, 46].

In three (18%) of the case reports, hypoglycemia resulted from interactions between antidepressant agents and oral antidiabetic medications [42, 46]. In one patient who experienced hypoglycemia within 11 days of taking doxepin 75 mg/day, blood glucose levels stabilized when the dose of tolazamide was reduced from 1 g/day to 100 mg/day (i.e., 90% reduction in the oral antidiabetic

Table 1 Summary of case reports of hyperglycemia and hypoglycemia associated with antidepressant agents

Reference	Country	Year	Event	Medication (daily dose)	Patient Gender	Patient Age (years)	Patient Diabetes status and history	Time to onset	Highest or lowest blood glucose level: mg/dl (mmol/l)	Time to stable glucose levels	Antidepressant cluster[a]
Shrivastava and Edwards [44]	USA	1983	Hypoglycemia	Imipramine 200 mg	Male	50	No	6 days	57 (3.17)	7 days	Cluster 2
True et al. [42]	USA	1987	Hypoglycemia	Doxepin 75 mg	Female	71	Type 2 diabetes	11 days	32 (1.94)	4 days	Cluster 2
True et al. [42]	USA	1987	Hypoglycemia	Nortriptyline 125 mg	Female	59	Type 2 diabetes	4 days	50 (2.78)	Not specified	Cluster 3
Zogno et al. [46]	Italy	1994	Hypoglycemia	Maprotiline 50 mg	Female	75	Type 2 diabetes	6 days	75 (4.16)	14 days	Cluster 3
Deeg and Lipkin [43]	USA	1996	Hypoglycemia	Fluoxetine 20 mg	Male	53	Type 2 diabetes	4 months	42 (2.36)	1 day	Cluster 1
Warnock and Biggs [45]	USA	1997	Hypoglycemia	Nefazodone 200 mg	Female	54	Type 2 diabetes	1 week	41 (2.28)	7 days	Cluster 4
Isotani and Kameoka [47]	Japan	1999	Hypoglycemia	Maprotiline 30 mg	Female	39	Type 1 diabetes	10 days	65 (3.60)	7 days	Cluster 3
Pollak et al. [48]	Canada	2001	Hypoglycemia	Sertraline 50 mg	Female	82	No	25 days	32 (1.78)	1 day	Cluster 1
Marley and Rohan [37]	Australia	1993	Hyperglycemia	Mianserin 65 mg	Female	44	No	Not specified	176 (9.80)	Not specified	Cluster 3
Petty [40]	USA	1996	Hyperglycemia	Paroxetine 10 mg	Female	24	No	3 weeks	345 (19.17)	7 days	Cluster 1
Oswald et al. [17]	Belgium	2002	Hyperglycemia	Fluvoxamine 100 mg	Female	60	Type 2 diabetes	5 days	210 (11.67)	2 days	Cluster 1
Fisfalen and Hsiung [38]	USA	2003	Hyperglycemia	Mirtazapine 15 mg	Female	32	Type 2 diabetes	5 months	1,042 (57.89)	Not specified	Cluster 3
Chen et al. [34]	USA	2003	Hyperglycemia/ Ketoacidosis	Mirtazapine 45 mg	Female	44	No	2 months	404 (22.44)	3 days	Cluster 3
Sansone et al. [41]	USA	2003	Hyperglycemia	Sertraline 50 mg	Female	54	Type 2 diabetes	2 months	180 (10.00)	Not specified	Cluster 1
Derijks et al. [36]	The Netherlands	2005	Hyperglycemia	Imipramine 50 mg	Female	62	Type 2 diabetes	1 month	Not reported	2 days	Cluster 2
Mumoli and Cei [35]	Italy	2008	Hyperglycemia	Clomipramine 25 mg	Female	84	No	5 months	459 (25.50)	2 days	Cluster 1
Chen and Lopes [39]	Australia	2008	Hyperglycemia	Mirtazapine 30 mg	Male	37	No	1 month	419 (23.30)	5 days	Cluster 3

[a] See "Appendix" for antidepressant cluster classification based on high affinity for six receptor/transporter sites

dose) [42]. In addition, in a patient who presented with a blood glucose level of 50 mg/dl (2.78 mmol/l) after 4 days of receiving nortriptyline 125 mg/day, hypoglycemia was resolved after discontinuing chlorpropamide and the patient was discharged with a stable blood glucose level of 90–120 mg/dl (5.00–6.67 mmol/l) [42]. Another patient presented with a blood glucose level of 75 mg/dl (4.16 mmol/l) within 6 days of therapy with maprotiline while also receiving four tablets a day of the combination drug glyburide 2.5 mg/phenformin 25 mg [46]. In that patient, hypoglycemia was resolved when the dose of maprotiline was reduced from 50 to 25 mg/day and the antidiabetic medication was reduced from four tablets to two tablets a day. The last blood glucose level recorded while the patient was on this therapy was 188 mg/dl (10.44 mmol/l) [46].

Weight changes were reported in five of the seventeen cases [38, 40, 41, 43, 45]. Table 2 shows the weight changes following antidepressant therapy. Most of the case reports did not report baseline weight, making it impossible to compute the percentage weight changes following antidepressant use. Use of mirtazapine, which caused significant elevation of plasma glucose levels, was accompanied by a significant weight gain of 15.9 kg over 5 months of treatment in one case report [38]. However, significant weight loss was reported with nefazodone, paroxetine, and fluoxetine. In one patient who presented with hypoglycemia, use of nefazodone was accompanied by a weight loss of 3.2 kg after 8 weeks of treatment [45]. Similarly, fluoxetine use was followed by hypoglycemia accompanied by a weight loss of 13 kg over 4 months of treatment [43]. In contrast, use of paroxetine resulted in a weight loss of 9.1 kg after 3 weeks of therapy, but was accompanied by hyperglycemia [40]. Similarly, sertraline was associated with a weight loss of 1.8 kg after 2 months in a patient who experienced hyperglycemia [41].

Discussion

The 17 published case reports suggest that antidepressants may cause both hyperglycemia and hypoglycemia. It is important to note that case reports do not provide evidence for causation. However, these findings appear to be consistent with a recent observational study by Derijks et al. [9]. Although no clear pattern between antidepressant class (i.e., tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRI], serotonin-norepinephrine reuptake inhibitors [SNRIs], and other antidepressants) and hyperglycemia or hypoglycemia was observed in this review of case reports, the study by Derijks et al. showed that the propensity to cause hyperglycemia or hypoglycemia was dependent on the pharmacological properties of individual antidepressant agents (see "Appendix") rather than a class effect [49, 50]. In that study, hyperglycemia was most pronounced in antidepressants with binding properties for the 5-HT_{2c} receptor (serotonin), H_1-receptor (histamine), and norepinephrinic reuptake transporter [9, 10]. In contrast, hypoglycemia was most pronounced in antidepressants with binding properties for the serotonin reuptake transporter [9, 10]. In another study, antidepressants with a high affinity for the serotonin reuptake transporter were associated with a trend toward increased risk for hypoglycemia (OR = 1.37; 95% CI: 0.71–2.62) [8].

The apparent lack of a class effect observed in these case reports appears to support Derijks et al.'s hypothesis that the effect of antidepressants is dependent on the pharmacologic properties of individual antidepressant agents [8, 9]. When antidepressants were classified into four clusters (see "Appendix") as proposed by Derijks et al., a pattern of the type of glucose dysregulation was observed for Cluster 1, Cluster 2, and Cluster 3. Antidepressants falling in Cluster 1 (i.e., clomipramine, fluoxetine, fluvoxamine, nortriptyline, paroxetine, and sertraline) tended to cause both hyperglycemia and hypoglycemia. Antidepressants falling in Cluster 2 (i.e., doxepin and imipramine) tended to cause hypoglycemia while those in Cluster 3 (i.e., maprotiline, mianserin, and mirtazapine) tended to cause hyperglycemia. Due to limited information, no clear pattern was observed between antidepressants falling in Cluster 4 (i.e., nefazodone) and type of glucose dysregulation. In addition, no clear pattern was noted between specific antidepressant agents and the time of onset of glucose dysregulation.

Table 2 Weight changes during antidepressant therapy

Reference	Medication (daily dose)	Timeline	Weight change (kg)
Sansone et al. [41]	Sertraline 50 mg	6 weeks	−1.8
Warnock and Biggs [45]	Nefazodone 200 mg	8 weeks	−3.2
Petty [40]	Paroxetine 10 mg	3 weeks	−9.1
Deeg and Lipkin [43]	Fluoxetine 20 mg	4 months	−13.0
Fisfalen and Hsiung [38]	Mirtazapine 15 mg	5 months	+15.9

The observations from the 17 case reports are supported by evidence from randomized controlled trials that have reported both hyperglycemic and hypoglycemic effects of antidepressant agents. Furthermore, in individuals without diabetes, use of antidepressants has been observed to be associated with a significant increase in the risk of hyperglycemia and diabetes [5–7]. In contrast to the case reports and the studies by Derijks et al., the evidence from randomized controlled trials in patients with diabetes appear to suggest that the effect of antidepressants on glycemic control differs according to antidepressant class. In these clinical trials, use of selective serotonin reuptake inhibitors (SSRIs) and bupropion resulted in a decrease in plasma glucose levels leading to improvements in glycemic control [51–55], while treatment with tricyclic antidepressants (TCAs) was associated with hyperglycemia and worsening of glycemic control [52].

The potential effects of antidepressants on glucose regulation observed in the case reports has clinical implications in individuals with diabetes and those at risk of developing diabetes. In particular, the potentiation of hypoglycemic effects of oral antidiabetic drugs by nortriptyline, doxepin and maprotiline warrants careful monitoring of glucose levels and adjustments of doses of antidiabetic medications accordingly in patients with co-morbid depression and diabetes mellitus. Furthermore, patients at high risk of developing diabetes should be closely monitored for glucose dysregulation when taking antidepressants, especially those using them on a chronic basis. Based on the published case reports, women appear to be more likely to develop glucose dysregulation when taking antidepressants and thus may require more rigorous monitoring than men. However, the disproportionally higher number of case reports in women may be related to their health seeking behavior. In addition, the lifetime prevalence of depression in women is approximately double that of men, making them more likely to receive antidepressant agents [56, 57].

Although only three reports were made in the last three decades, use of mirtazapine appears to be associated with the propensity to cause hyperglycemia and diabetes mellitus [34, 38, 39]. Given the established association between mirtazapine and significant weight gain, it was not surprising that mirtazapine ($n = 3$) had the highest number of case reports of hyperglycemia, with glucose levels ranging from 404 to 1,042 mg/dl (22.44–57.89 mmol/l) [58–60]. In contrast, the hypoglycemia noted with maprotiline was not consistent with an increase in weight gain observed in several studies [46, 47, 61].

Several limitations need to be taken into account when interpreting the findings of this review. First, causation cannot be inferred from case report findings. Although there was a clear temporal relationship between the introduction of antidepressant agents and glucose dysregulation in all of the case reports, the lack of controls makes it difficult to conclude with certainty that the glucose regulation disturbances resulted from the initiation of antidepressant agents. Second, neither incidence nor prevalence of hyperglycemia and hypoglycemia can be computed from case reports. Third, the small number of cases reported over the last three decades may suggest that these adverse drug events were unique to the patients reported in these case reports, which could potentially introduce selection bias. Fourth, it is unlikely that all adverse drug events will be published as case reports, therefore introducing publication bias. Despite the reported effects of these drugs on appetite, lack of information on weight changes following antidepressant therapy in most of the case reports limits the interpretation of these findings as the changes in glucose regulation may have been related to lifestyle changes following improvements in mood.

Notwithstanding the limitations outlined above, this review of case reports provides unique data about the type of glucose control disturbances that may occur during treatment with various antidepressant agents. A detailed analysis of the characteristics of real-life patients with different clinical presentation profiles provides a better understanding of unique patient characteristics that may play a role in determining the type of glucose dysregulation following antidepressant therapy. More importantly, this review serves to generate hypotheses about patient characteristics that may be risk factors for glucose dysregulation during treatment with antidepressants.

Conclusion

It is not clear from published case reports whether changes in glucose regulation following antidepressant therapy initiation are due to antidepressants or changes in mood and lifestyle. Due to the limited number of case reports, it was not possible to identify patients at high risk of developing glucose dysregulation. Given the limitations of case reports in establishing causation and the ambivalence in observational studies regarding the association between antidepressants and glucose dysregulation, more research is needed to establish whether changes in glucose regulation following antidepressant therapy are as a result of medications or changes in mood and lifestyle.

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Conflicts of interest The authors have no conflicts of interests to declare.

Appendix

See Table 3.

Table 3 Classification of selected antidepressant agents on high binding affinity for receptor/transporter sites as proposed by Derijks et al. [10]

Antidepressant agent	Classification by molecular structure and pharmacological mechanism of action	Classification based on high binding affinity for six receptor/transporter sites[a]
Amitriptyline	TCA	Cluster 2
Bupropion	NDRI	Cluster 4
Citalopram	SSRI	Cluster 1
Clomipramine	TCA	Cluster 1
Doxepin	TCA	Cluster 2
Duloxetine	SNRI	Cluster 1
Escitalopram	SSRI	Cluster 1
Fluoxetine	SSRI	Cluster 1
Fluvoxamine	SSRI	Cluster 1
Imipramine	TCA	Cluster 2
Maprotiline	TeCA	Cluster 3
Mianserin	TeCA/NaSSA	Cluster 3
Mirtazapine	NaSSA	Cluster 3
Nefazodone[b]	SARI	Cluster 4
Nortriptyline	TCA	Cluster 3
Paroxetine	SSRI	Cluster 1
Reboxetine	NRI	Cluster 4
Sertraline	SSRI	Cluster 1
Trazodone	SARI	Cluster 4
Venlafaxine	SSRI	Cluster 1

Adapted from Derijks et al. [10]

NaSSA norepinephrine and serotonin specific with alpha-2 antagonist properties, *NDRI* norepinephrine dopamine reuptake inhibitor, *NRI* selective norepinephrine reuptake inhibitor, *TCA* tricyclic antidepressant, *TeCA* tetracyclic antidepressant, *SARI* serotonin-2 antagonist/reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a] Six receptor/transporter sites: 5-HT (serotonin) reuptake transporter, norepinephrine reuptake transporter, 5-HT_{2c} receptor, M_3-receptor (muscarinic), H_1-receptor (histamine), alpha-1 receptor

[b] Brand name nefazodone (Serzone) discontinued in 2004 due to cases of hepatotoxicity. Generic nefazodone is still on the market. Classification by high binding affinity for receptor/transporter sites:

Cluster 1: high binding affinity for 5-HT reuptake transporter

Cluster 2: high binding affinity for all six binding sites

Cluster 3: high binding affinity for H_1-receptor and 5-HT_{2c} receptor

Cluster 4: no specific similarities within and outside the cluster in terms of the binding affinity for the six receptor/transporter sites

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