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ORIGINAL RESEARCH

Sertraline for the Treatment of Major Depressive Disorder in the US: Effectiveness and Acceptability in Real-World Practice

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Background: Major depressive disorder (MDD) is a serious mental illness and leading cause of disability. MDD is highly comorbid with physical illnesses such as cardiovascular disease (CVD) and diabetes mellitus (DM). Sertraline, a selective serotonin reuptake inhibitor, is proven effective and well-tolerated in clinical trials, and is recommended among first-line treatment options for MDD.

Methods: This study explored the effectiveness and acceptability of sertraline in real-world clinical practice, utilizing electronic health record-derived, de-identified data from NeuroBlu Data in the USA. All-cause sertraline discontinuation was the main outcome, with change in Clinical Global Impressions Severity (CGI-S) serving as a secondary outcome.

Results: All-cause discontinuation was assessed in 2948 patients treated with sertraline for MDD (702 comorbid with CVD and 280 with DM). The cumulative discontinuation rates at 2- and 3-month follow-up time points were 16.9% and 24.8%, respectively. No significant differences were observed between males and females or those with and without CVD or DM. Change in CGI-S was assessed in 713 patients who had data for one or more follow-up assessments conducted between 2 to 24 months after sertraline prescription. About 9% to 17% of patients demonstrated clinically *substantial* improvement in CGI-S (decrease by ≥2) across follow-up time points, while 74% to 88% showed little or no change. A sensitivity analysis showed clinically *meaningful* improvement in CGI-S (decrease by ≥1) in 19% to 36% of patients, with 54% to 69% showing no change. Patients with greater illness severity at baseline were more likely to experience improvement.

Conclusion: This study demonstrates that all-cause discontinuation rates in routine practice were consistent with clinical trials indicating comparable sertraline treatment acceptability. The findings add to the body of evidence on real-world effectiveness and clinical utility of sertraline in patients with MDD with or without comorbid chronic medical illnesses like CVD and DM.

Plain Language Summary: Major depressive disorder (MDD) is a serious health condition affecting many people worldwide. People with MDD often have other health problems such as heart disease and diabetes. Sertraline is a commonly used treatment for MDD, which may be prescribed in the presence of these other health issues.

This study used the medical records of about 3000 adults with MDD living in the US to explore whether they benefitted from treatment with sertraline. The main way this was measured was using "all-cause discontinuation rate". This looks at how many people stopped taking sertraline for any reason and is considered a measure of how well the medicine worked and how it was tolerated. Most people continued taking sertraline during the study period, with 17% of people stopping it after 2 months; a further 8% had stopped it at 3 months. People with MDD and other illnesses like heart disease or diabetes were just as likely to keep taking sertraline as those without.

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The overall severity of depressive illness was not high in most people studied when they started taking sertraline and only small changes were observed with treatment. Patients with more severe illness were more likely to improve when treated with sertraline.

Overall, patients with MDD in this study responded to treatment with sertraline. However, when studies use data from medical records that have been collected for other reasons, more studies are needed to confirm the results.

Keywords: antidepressants, Clinical Global Impression – Severity, major depressive disorder, real-world evidence, sertraline, United States

Introduction

Major depressive disorder (MDD) is a serious mental illness and a leading cause of disability worldwide,[1–3] with a lifetime prevalence reported to range from 2% to 21%.[4] The World Health Organization estimates that by 2030 MDD will be associated with the highest disease burden of all conditions and will be the greatest cause of disability.[5,6] In the US, MDD is one of the most common mental health disorders, with a lifetime prevalence of approximately 20%,[7] and an estimated 21 million US adults experienced at least one episode of MDD in 2021.[1,8]

MDD is highly comorbid with physical illness, with two of the most common conditions being cardiovascular disease (CVD) and diabetes mellitus (DM).[9–12] In the US, the estimated prevalence of comorbid MDD is 11% among patients with DM, and 15–20% among patients with CVD.[9] The relationship is bidirectional, with an estimated prevalence of 6.5% for DM in people with MDD,[11] and people living with MDD also have an elevated risk of metabolic syndrome[13] and are at significantly greater risk of adverse cardiovascular outcomes than the general population.[14]

Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line treatment for MDD.[15–17] The SSRI sertraline was first approved in the US for the treatment of MDD in 1991 after its efficacy and safety were established in clinical trials.[18–22] Subsequently, sertraline's real-world effectiveness has also been demonstrated across several studies.[23–25] However, knowledge gaps remain, with real-world evidence (RWE) becoming increasingly important for addressing these, particularly regarding effectiveness and safety in those subgroups of patients who are often systematically excluded from randomized controlled trials (RCTs).[26–28]

Several measurement scales are used in RCTs to determine the efficacy of medications in MDD, the most common of which are the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS).[29] However, these interview-based instruments are rarely used in routine clinical care settings. Another scale commonly used in clinical trials is the Clinical Global Impressions Severity (CGI-S) scale, a physician-reported global measure of the severity of overall disease,[30] which can be completed in less than a minute by an experienced rater.[30] However, while these are important tools recommended for use beyond clinical trials,[17,31] measurement-based care is not consistently employed in routine clinical practice.[29,32–34] Therefore, efficacy endpoints utilized in the clinical trial setting are not always available in real-world practice, thus other measures are needed to determine the effectiveness of treatments in a real-world setting.[35,36]

One such measure is all-cause discontinuation, which has been utilized in MDD as a measure of treatment acceptability. Specifically, in a dataset that included 81 RCTs and >13,000 participants, all-cause discontinuation rates demonstrated that all treatments assessed among patients with MDD were more acceptable than placebo.[37] Additionally, in a systematic review and meta-analysis including placebo-controlled and head-to-head trials of 21 antidepressants, high all-cause discontinuation rates were associated with a lower response to treatment.[38] More recently, a real-world retrospective cohort study that included >600,000 patients with depression utilized all-cause discontinuation to compare acceptability between antidepressants and to compare these with RCT findings.[39]

To explore effectiveness and acceptability of sertraline in real-world clinical practice in the US, the current study utilized electronic health records (EHR) from NeuroBlu Data, using all-cause discontinuation of sertraline as the main outcome measure, with change in CGI-S and healthcare resource utilization (HCRU) as secondary outcomes.

Methods

Study Design and Data Source

This retrospective cohort study utilized EHR-derived, de-identified data from NeuroBlu Data, a longitudinal behavioral health real-world database,[40] comprising structured and unstructured patient-level clinical data from healthcare providers in the US (including academic medical centers, community mental health clinics, nonprofit health systems, private practices and specialized substance use treatment centers). The database version used in the study (23R5) captures approximately 1,500,000 patients and covers records between January 1, 1999, and September 30, 2021.

Patient data from NeuroBlu Data are de-identified at source, thus institutional review board approval was not necessary for this study. NeuroBlu Data has received a waiver of authorization for analysis of de-identified healthcare data from the WCG Institutional Review Board (Ref: WCG-IRB 1–1470336-1).

Patient Population

Patients in NeuroBlu Data were included in the current study if they had at least one prescription record for sertraline (index date defined as the date of first recorded Zoloft [sertraline] prescription), at least one recorded diagnosis for MDD (see Supplementary Table 1 for disease definitions) at baseline (defined as ±14 days from the index date) and were aged ≥18 years at the time of first sertraline prescription (Figure 1).

Patients were excluded if their EHR had no information on sex or it was unknown, if they had psychiatric diagnoses other than MDD or anxiety disorder at baseline (ie, all anxiety disorders were allowed as comorbid conditions to a primary MDD diagnosis), or if there was a record of any psychoactive medications other than sertraline at baseline (except for anxiolytics, sedatives/hypnotics, or analgesics).

Overall, two patient cohorts were defined using criteria designed to address the research questions for each specified outcome (Figure 1). Population A, utilized for assessing the primary outcome of all-cause sertraline discontinuations at 2 and 3 months, met all the criteria outlined above and further comprised patients who had ≥150 days of follow-up data (defined as any record of clinical activity) and a sertraline prescription of ≥14 days. All assessments in this population were stratified by CVD status, DM status, and sex. Patients with CVD were those with at least one recorded CVD International Classification of Disease [ICD] code or at least one medication prescription used to manage CVD at or 12 months prior to baseline. Patients with DM were those with at least one recorded DM ICD code or at least one medication prescription indicated for clinical management of DM at or 12 months prior to baseline (see Supplementary Table 1 for disease definitions and Supplementary Table 2 for medication lists).

The second cohort, termed population B (utilized for assessing the secondary outcome of CGI-S change), also met all the criteria outlined above, and further comprised patients who had CGI-S measurements available at both baseline and in at least one follow-up period (2, 3, 6, 9, 12, 18 and 24 months), and who had a recorded sertraline prescription duration of ≥2 months.

Exposure

Sertraline exposure was defined as at least one prescription record for sertraline. Consecutive prescriptions were merged into a single continuous prescription where the gap between prescriptions was ≤60 days; a patient was considered to have discontinued sertraline if no prescription was recorded for more than 60 days.

Outcomes

Demographic and clinical characteristics of patients with MDD prescribed sertraline in NeuroBlu Data were assessed in both population A and B. The following variables were collected: baseline demographics (age, gender, race), specific anxiety disorder subtypes (including agoraphobia, panic disorder, and social phobia), sertraline dosage intensity, cardiovascular and antidiabetic medication history (including glucagon-like peptide 1 [GLP-1] agonists and insulin), and healthcare utilization metrics defined by the frequency of outpatient, inpatient, and emergency room visits at 2- and 3-months' follow-up.

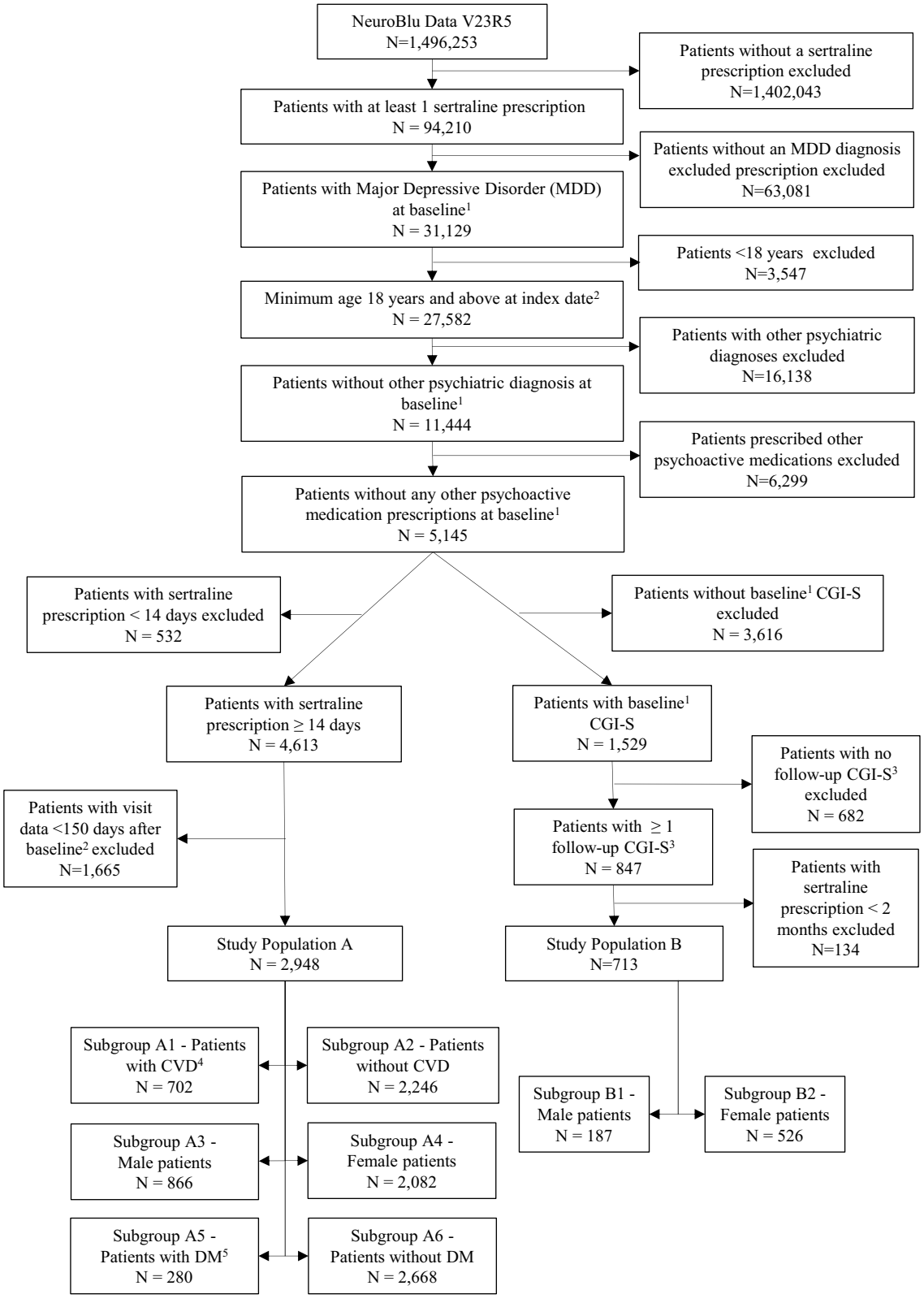

Figure 1 Patient population flowchart. [1] Baseline is defined as ±14 days from the index date (inclusive). [2] Index date is defined as the date of first recorded sertraline prescription. [3] Follow-up periods: ±14 days of 2, 3, 6, 9, 12, 18, 24 months from the baseline. [4] At least 1 recorded cardiovascular disease code at or 12 months prior to baseline. [5] At least 1 recorded diabetes mellitus code at or 12 months prior to baseline.

Note: It is possible for patients to be included in both the primary and secondary outcome populations; these are not mutually exclusive (total overlap: 585 patients (19.8% of population A & 82.0% of population B)).

In addition to the primary outcome of all-cause discontinuation of the first sertraline prescription, population A was also used to evaluate HCRU, including outpatient, inpatient, and emergency department (ED) visits.

Population B was used to assess the secondary outcome of change in illness severity, utilizing CGI-S, in patients with MDD during follow-up. Change in illness severity was described using CGI-S at the time of first sertraline prescription and at follow-up at 2, 3, 6, 9, 12, 18, and 24 months, stratified by sex. CGI-S is a 7-point scale where each value describes patient state as follows: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients.

A 2-point change in CGI-S was considered a clinically *substantial* change, as such a change has been shown to correlate with clinically substantial change on the Montgomery-Åsberg Depression Rating Scale (MADRS; 12-point change), the Sheehan Disability Scale (SDS; 8-point change), and the Patient Health Questionnaire-9 (PHQ-9; 6-point change) in patients with treatment-resistant depression.[41] Change in severity was categorized as follows: improvement if CGI-S decreases by ≥2 points from baseline; little or no change if CGI-S does not change by more than 1 point in any direction; worsening if CGI-S increases by ≥2 points from baseline.

In sensitivity analysis (see section "Data analysis"), a 1-point change on CGI-S was considered as clinically *meaningful* change, correlating with 6-, 4, and 3-point changes from baseline on the MADRS, SDS and PHQ-9 shown in one study,[41] and a reduction of 8–9 points on the MADRS in a second study.[42] The full definition of clinically *meaningful* change was: improvement if CGI-S decreases by ≥1 point from baseline; little or no change if CGI-S does not change in any direction by ≥1 point; worsening if CGI-S increases by ≥1 point from baseline.

Data Analysis

In population A, the proportion of patients who discontinued treatment at 2 months and at 3 months was assessed. Patients were censored if a psychiatric diagnosis other than MDD and anxiety disorder or a prescription of psychoactive medications other than anxiolytics, sedatives/hypnotics or analgesics was recorded during follow-up (see Supplementary Table 1 for disease definitions and Supplementary Table 2 for medication lists). Differences between patient subgroups in all-cause discontinuation rate at these times were assessed using a non-parametric Log rank test.

HCRU, during 2 and 3 months following the first sertraline prescription, was assessed for population A by calculating the number of outpatient, inpatient, and ED visits in these periods; if an ED visit transitioned into an inpatient stay, this was captured in both categories.

For the secondary outcome of change in CGI-S, proportion of patients in population B observed with each type of change was reported. A sensitivity analysis was performed against a definition of "clinically *meaningful* change". A further sensitivity analysis was conducted to assess change among patients with different illness severity at baseline, categorized based on CGI-S score as follows: 1–3 = mildly ill; >3-5 = moderately ill; >5-7 = severely ill.

For each follow-up period, only those patients with CGI-S data at baseline and at the respective follow-up time point were included. At each follow-up time point (2, 3, 6, 9, 12, 18, and 24 months), patients who did not have a CGI-S measurement were censored. For all analyses, statistical significance was assumed at $p < 0.05$.

For continuous data, groups were compared using Mann Whitney *U*-tests, while for categorical data Chi-square test of independence was used, utilizing Fisher's exact test instead when a category value had <5 counts. All tests were two-sided with alpha = 0.05, without multiple comparison adjustments.

Results

Baseline Demographics and Clinical Characteristics

A total of 94,210 patients with at least one sertraline prescription were selected from NeuroBlu Data, of whom 27,582 were aged at least 18 years and had MDD at baseline (Figure 1). After excluding patients with other psychiatric diagnoses and those prescribed any other psychoactive medication, a total of 5145 patients were identified. From these patients, population A was identified, comprising a total of 2948 patients (Table 1). Of these patients, 702 patients had CVD, 280 patients had DM, and there were 866 male patients. Population B, also identified from within the 5145 patients noted above, comprised a total of 713 patients (Table 1); this included 187 male patients and 526 female patients.

Table 1 Baseline Demographic and Clinical Characteristics

Variable	Population A							Population B		
	Total (n = 2948)	with CVD (n = 702)	No CVD (n = 2246)	with DM (n = 280)	No DM (n = 2668)	Male (n = 866)	Female (n = 2082)	Total (n = 713)	Male (n = 187)	Female (n = 526)
Age, years (SD)	41 (15.46)	53 (13.72)	37 (13.91)*	53 (13.77)	40 (15.10)**	43 (15.41)	40 (15.43)#	43 (16.25)	45 (16.11)	43 (16.28)
Gender, n (%)										
Male	866 (29)	196 (28)	670 (30)	71 (25)	795 (30)	–	–	187 (26)	–	–
Female	2082 (71)	506 (72)	1576 (70)	209 (75)	1873 (70)	–	–	526 (74)	–	–
Race, n (%)										
White	1200 (41)	158 (23)	1042 (46)	53 (19)	1147 (43)	375 (43)	825 (40)	388 (54)	101 (54)	287 (55)
Black or African American	1257 (43)	455 (65)	802 (36)	193 (69)	1064 (40)	360 (42)	897 (43)	61 (9)	16 (9)	45 (9)
Other race	96 (3)	24 (3)	72 (3)	11 (4)	85 (3)	26 (3)	70 (3)	22 (3)	3 (2)	19 (4)
Unknown	395 (13)	65 (9)	330 (15)	23 (8)	372 (14)	105 (12)	290 (14)	242 (34)	67 (36)	175 (33)
Clinical characteristics at baseline, n (%)										
Comorbid anxiety	747 (25)	168 (24)	248 (39)	57 (20)	690 (26)**	185 (21)	562 (27)#	257 (36)	62 (33)	195 (37)
Concomitant Anxiolytics, analgesics, hypnotics/sedatives	1110 (38)	273 (39)	837 (37)	109 (39)	1001 (38)	306 (35)	804 (39)	272 (38)	57 (30)	215 (41)¶
Sertraline dose, n (%)					**		#			
≤25	909 (31)	233 (33.19)	676 (30.10)	105 (37.50)	804 (30.13)	216 (24.94)	693 (33.29)	99 (13.88)	20 (10.70)	79 (15.02)
26-50	1491 (51)	355 (50.57)	1136 (50.58)	134 (47.86)	1357 (50.86)	482 (55.66)	1009 (48.46)	326 (45.72)	85 (45.45)	241 (45.82)
51-100	440 (15)	86 (12.25)	354 (15.76)	30 (10.71)	410 (15.37)	129 (14.90)	311 (14.94)	257 (36.04)	74 (39.57)	183 (34.79)
101-150	28 (1)	7 (1.00)	21 (0.93)	0 (0.00)	28 (1.05)	10 (1.15)	18 (0.86)	11 (1.54)	2 (1.07)	9 (1.71)
>150	37 (1)	8 (1.14)	29 (1.29)	4 (1.43)	33 (1.24)	14 (1.62)	23 (1.10)	20 (2.81)	6 (3.21)	14 (2.66)
Unknown	43 (1)	13 (1.85)	30 (1.34)	7 (2.50)	36 (1.35)	15 (1.73)	28 (1.34)	99 (13.88)	20 (10.70)	79 (15.02)

Note: All data presented as mean (SD) unless otherwise stated. *P < 0.05 vs patients with CVD; **P < 0.05 vs patients with DM; #P < 0.05 vs male patients (population A); ¶P < 0.05 vs males (population B).
Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; SD, standard deviation.

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All-Cause Discontinuation

At 2 months' follow-up, 16.9% of patients had discontinued sertraline treatment, 62.1% were continuing their initial sertraline prescription, and the remaining patients had a censoring event (8.5% had a different psychiatric diagnosis recorded and 12.5% had a different psychiatric medication prescription) (Figure 2a). At 3 months' follow-up, discontinuation was recorded in 24.8% of patients, 49.7% of patients were still receiving sertraline, and the remaining patients had a censoring event (another psychiatric diagnosis in 10.6% and another psychiatric prescription in 14.9%) (Figure 2a).

Discontinuation rates, at both 2 and 3 months, were comparable between male and female patients (18.1% vs 16.4% and 24.9% vs 24.7%, respectively) (Figure 2b). Furthermore, there were no statistically significant differences in discontinuation rates between patients with and those without CVD comorbidity at 2 months (15.2% vs 17.4%) or at 3 months (26.2% vs 24.4%), or between patients with and those without DM at 2 months (13.2% vs 17.3%) or at 3 months (26.4% vs 24.6%) (Figure 2b).

Healthcare Resource Utilization

Outpatient visits were more common than ED or inpatient visits in all subgroups (Figure 3). Patients with DM or CVD had significantly more outpatient visits than those without DM or CVD, respectively, as well as more emergency room visits (although absolute numbers were very small), all $p < 0.05$. (Figure 3) There were no significant differences between groups for inpatient visits (data not shown). Altogether, 66% of all outpatient visits were labelled as psychiatric visits based on place of service, diagnoses, procedures and prescriptions recorded during the visit. ED and inpatient visits were very rare, with a mean of <1 overall and in all patient subgroups.

CGI-S

Overall, the change in CGI-S during the study period was relatively low (Figure 4). On the per protocol analysis looking at clinically *substantial* change in CGI-S, illness severity remained stable (little or no change in CGI-S) for the majority of patients at all time points – over 80% of patients remained stable at all time points, with the exception of the 12-month time point (74%). The rates of improvement recorded ranged between 9% and 17%, and worsening in CGI-S scores was recorded in 2% to 9% of patients at different follow-up time points.

Sensitivity Analyses

In the sensitivity analysis looking at clinically *meaningful* change in CGI-S, more than half of all patients with MDD had stable illness severity, with little or no change in CGI-S at 2 months for 57% of patients, with values at time points 3–24 months ranging from 54% to 69%. At 2 months, improvement was recorded for 36% of patients, with values at time points 3–24 months in the range of 19% to 33%. The rates of worsening were recorded in the range of 8% to 18% of patients. Across the different categories of illness severity, 41% of patients with moderate/severe baseline CGI-S ($n = 93$) experienced improvement in illness severity, compared with 12% of those with mild baseline CGI-S ($n = 6$) ($p < 0.05$). A similar pattern was observed at other time points as well. These changes in CGI-S, at baseline and follow-up were not significantly different between males and females at any of the follow-up time points.

Discussion

In this US-based, real-world patient population, all-cause discontinuation rates at 2 months and at 3 months suggest good general acceptability of sertraline among US patients receiving routine clinical care. The overall all-cause discontinuation rates of 16.9% and 24.8% at 2 and 3 months, respectively, are broadly consistent with all-cause discontinuation rates reported for sertraline across RCTs.[43–47] For example, a large meta-analysis looking at 21 antidepressants reported sertraline all-cause discontinuation rates that ranged from approximately 10% to 37% over 6–24 weeks.[38,48] In terms of real-world discontinuation rates due to adverse events for the SSRIs, a recent retrospective cohort study that included more than 20,000 participants receiving antidepressant treatment in the past 4 years reported discontinuation due to adverse effects for SSRIs in the range of approximately 39% to 48%.[49]

In a pooled analysis of data for women of child-bearing age from nine clinical trials of sertraline, all-cause discontinuation rates of 38.2% for sertraline and 35.2% for placebo at 8 weeks were reported.[50] In the current study,

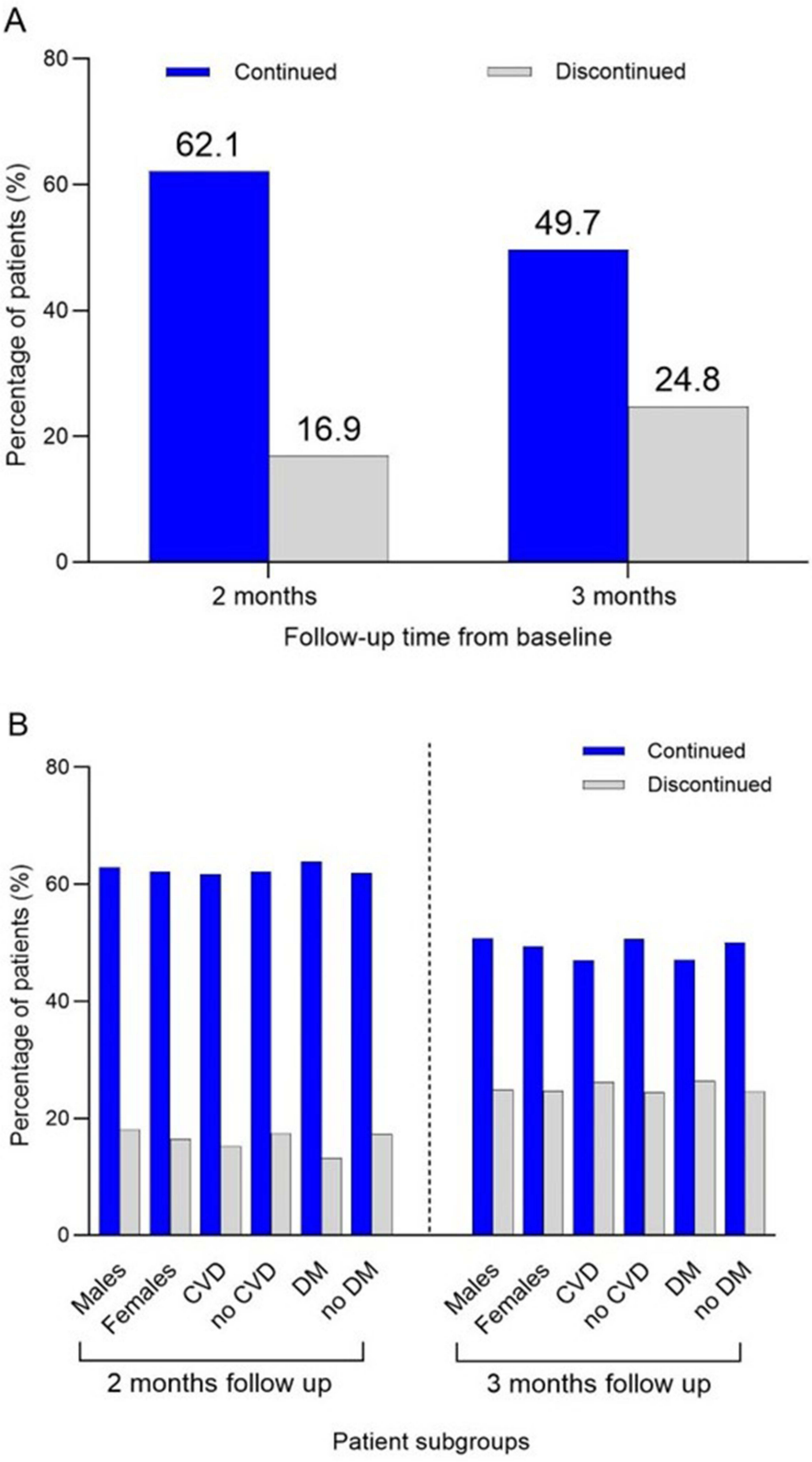

Figure 2 All-cause discontinuation at 2 months' and 3 months' follow-up from baseline (defined as ±14 days from the index date, inclusive) for (**A**) all patients and (**B**) by patient subgroup.
Note: percentages do not add up to 100% as patients excluded due to censoring events are not shown.
Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus.

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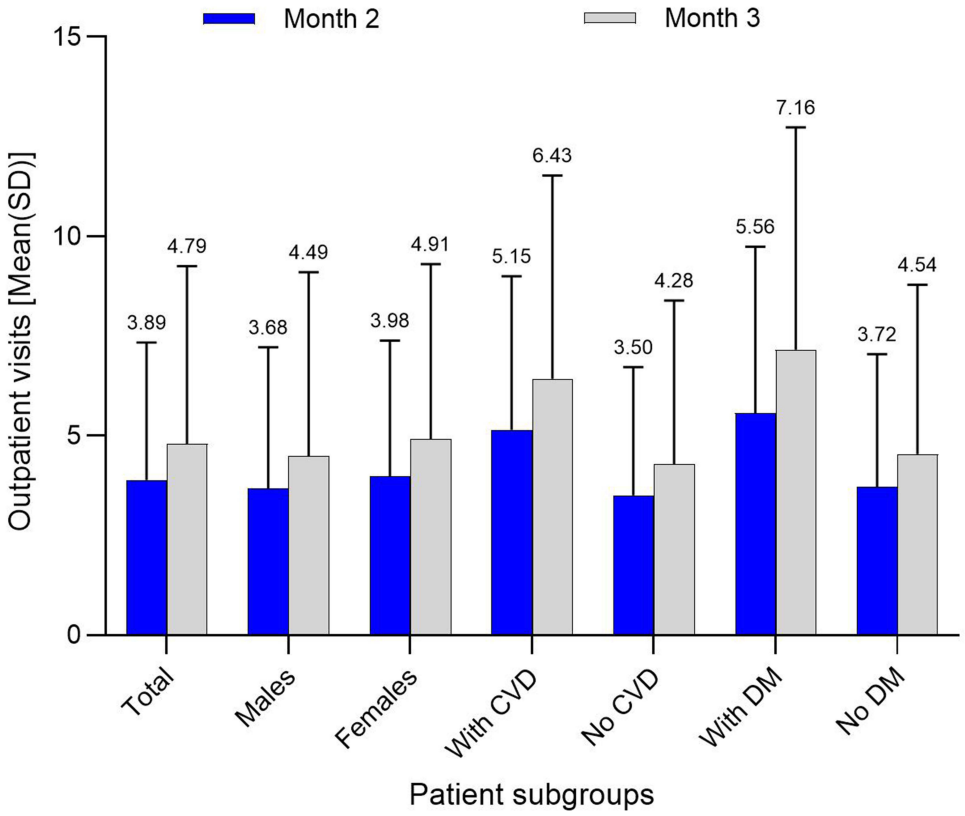

Figure 3 Mean number of outpatient visits baseline (defined as ±14 days from the index date, inclusive) to month 2 and baseline to month 3, for population A, overall and stratified by patient subgroup.
Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; SD, standard deviation.

the all-cause discontinuation rate at 2 months in female patients was 16.4%, which is lower than that observed in RCTs. The difference may be driven by greater flexibility in adjusting treatment in routine care or patients in the real-world having lower baseline illness severity.

Overall, these sertraline all-cause discontinuation findings provide meaningful information regarding its acceptability in real-world use, as maximum clinical improvement is typically observed after 2 to 6 months of treatment with antidepressant medications, and premature discontinuation of antidepressant therapy is associated with an increased risk of MDD relapse.[51]

Importantly, the demographic and clinical characteristics of the patients included in this study are largely consistent with known information regarding patients with MDD in the US.[52,53] The majority of patients were female, in line with previously documented MDD prevalence rates, with patients having CVD or DM typically being older.[52–55] In the analysis of the primary outcome population, the distribution between White and Black/African-American patients was relatively balanced, with these two groups collectively accounting for over 80% of the population. Of note, there were more Black/African-American individuals in subgroups of patients with CVD or DM comorbidities, highlighting the potential association between racial demographics and the prevalence of these comorbid conditions.[56,57] In contrast, in the secondary outcome population there was a significantly higher proportion of White and patients of unknown race. This variation is largely attributed to the specific data requirements of this population, particularly the inclusion of CGI-S data, which was captured predominantly by a single data partner within NeuroBlu Data. The racial composition of this secondary outcome population, therefore, likely reflects the demographic profile served by the associated healthcare provider.

Outpatient visits were the primary form of HCRU, peaking in the first two months, with very few ED or inpatient visits across all patient subgroups. As expected, patients with MDD and comorbid CVD or DM had significantly higher HCRU than patients with MDD without such comorbidity, yet all-cause discontinuation rates for sertraline did not differ significantly between subgroups. This finding is important, as it suggests that sertraline is an effective treatment for

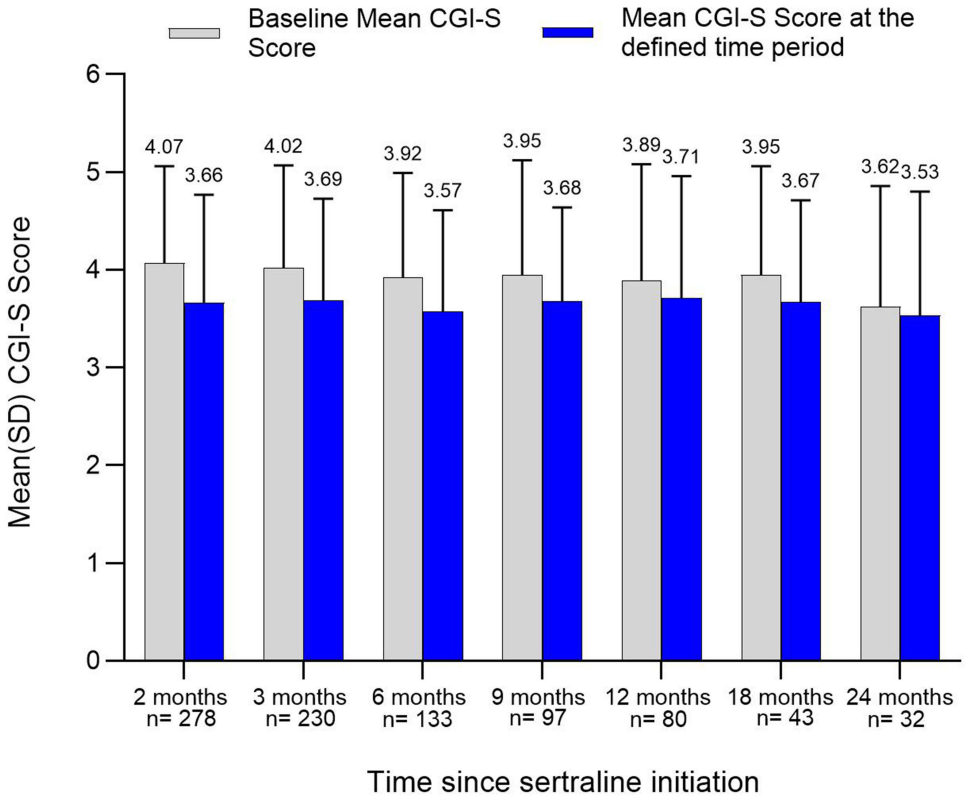

Figure 4 Mean CGI-S at baseline (defined as ±14 days from the index date, inclusive) and at corresponding follow-up periods.
Abbreviation: CGI-S, Clinical Global Impressions – Severity.

patients with MDD with comorbid CVD or DM.[9] The fact that outpatient visits were significantly higher among patients with MDD with CVD/DM than in those without CVD/DM may be explained by bidirectional associations between these comorbidities and a more severe disease course associated with greater service utilization. However, our study based on EHR data was not designed to determine the cause for higher outpatient visits. If replicated, future studies should assess different reasons leading to outpatient visits. Of note, no differences in HCRU were seen between men and women.

The analysis on illness severity in these patients with MDD showed that most patients on sertraline treatment were at the lower end of moderately severe illness, with a median CGI-S score of 4. This moderate baseline illness severity, with very few patients with severe illness, makes it unlikely that clinically substantial variations in CGI-S would be seen following sertraline treatment. Therefore, we performed a sensitivity analysis that utilized a clinically meaningful change. Using this clinically meaningful change definition, a general trend towards improvement in illness severity was observed during the follow-up period, albeit with fluctuations of low magnitude. These findings suggest that overall, in a mild to moderately ill patient population with MDD, sertraline provides a modest but consistent benefit for many patients over time. We were also able to demonstrate that there were greater improvements in illness severity in people with greater MDD illness severity at baseline.

It is important to contextualize the CGI-S improvement rates observed here against those seen in RCT settings. While RCTs report response rates (typically defined as ≥50% reduction in HAM-D score) in the range of approximately 50–70%,[22,58] these trials specifically recruit patients with high baseline severity to maximize the detectability of treatment effects. In contrast, our real-world cohort presented with a median baseline CGI-S of 4 (moderately ill), likely creating a floor effect in a substantial number of subjects compared to RCTs where generally a CGI-Severity of 4 is the entry criterion. Therefore, achieving a 2-point substantial reduction in CGI-S scores from baseline is mathematically and clinically more difficult than in more severely ill populations. Consequently, the high proportion of patients showing little

or no change likely reflects a successful maintenance of stability (prevention of worsening), rather than treatment failure, an interpretation supported by the high treatment retention rates observed in the primary analysis.

It is possible that patients who experience significant improvement may be less likely to continue regular clinical visits, and those patients may not have been represented in our analyses, especially in those timepoints where longer periods of follow-up are considered. Additionally, it is important to highlight that as CGI-S is not routinely collected in standard care, patients were not recorded with CGI-S at every follow-up time point. Therefore, each time point represents a different subset of patients rather than a single cohort followed consistently throughout the study period. For example, a patient with CGI-S measured at baseline and at 9 months, but with no other CGI-S measurement, was only included in the 9-month follow-up data comparison. Moreover, while the availability of CGI-S data was primarily driven by the reporting practices of specific data partners, beyond site-specific availability, the required presence of baseline and follow-up CGI-S data inherently selects for patients with higher treatment engagement and monitoring frequency. Thus, patients who attend regular follow-up visits – allowing for longitudinal CGI-S capture – are likely more adherent to their treatment plan than those lost to follow-up. Because of these methodological limitations, along with the small sample size, caution is needed in interpreting these results, especially where longer follow-up is considered.

Interestingly, the recommended sertraline dose range for patients with MDD is 50–200 mg/day, whereas most patients in the current study were prescribed a starting dose of sertraline either below or at the minimum recommended dose (25 mg or 50 mg).[59] The duration of treatment on this low dose was not analyzed.

There are some additional limitations of the current study that should also be considered. In our study, all-cause discontinuation was used as a proxy measure of effectiveness and acceptability. While this approach lacks granularity, we believe the literature shows that all-cause discontinuation is an accepted effectiveness measure.[35,37–39] Additionally, data prior to sertraline initiation were not included, so there was no way to determine the reason for starting sertraline, with such reasons likely to include lack of efficacy or tolerability of prior treatments, as well as non-adherence in some patients, reasons that could be expected to affect the baseline MDD severity and patterns of response to sertraline. Furthermore, the use of EHR data has some inherent limitations, including that the data have not been systematically obtained for the purposes of this study and therefore may not be available for all variables measured across all individuals, therefore, data may be missing from structured data fields. Additionally, in EHR data, clinical history is only available from the time the patient has a first clinical contact with a mental healthcare provider, and therefore prior clinical history may not be well captured, and we cannot ascertain information on prior diagnoses or pharmacological treatments. Furthermore, NeuroBlu Data contains only prescription data, and adherence (via prescription claims) was not assessed. NeuroBlu Data mostly captures specialized healthcare centers and may not accurately represent patients with MDD who are managed in primary care. Finally, our analysis did not stratify patients by dosage. As the two-to-three-month study period coincides and overlaps with the standard titration phase of antidepressant therapy, dosage was treated as a time-varying factor that could not be categorized into static groups without introducing misclassification or survivorship bias. Consequently, we could not evaluate dose-dependent variations in efficacy or acceptability that are affected by insufficient efficacy and/or side effects in our analyses. Future studies with longer follow-up periods are recommended to assess these associations once stable maintenance dosing is achieved. Nevertheless, despite these limitations, this study of close to 3000 patients initiating sertraline treatment provides real-world evidence of the acceptability and some specific effectiveness outcomes within and across clinically important subgroups of patients with MDD.

Conclusion

The current study provides evidence that, in a real-world setting, all-cause discontinuation for sertraline is comparable with that seen in RCTs across multiple patient groups, namely patients with and without DM or CVD, as well as between males and females. The observation that sertraline appears acceptable and effective in patients with CVD or DM could reassure clinicians about its safety and applicability in populations with multimorbidity and polypharmacy who are often excluded from RCTs. Additionally, these reported real-world discontinuation rates can help guide shared decision-making and expectation-setting with patients, emphasizing that clinicians might realistically anticipate adherence and response and/or maintenance of stability over time. In this context, the higher outpatient visits in patients with DM or

CVD emphasize the need for closer monitoring of symptoms in the presence of these medical comorbidities. Finally, the fact that most patients either improved or remained stable with sertraline with long-term treatment suggests that that sertraline is an effective and acceptable treatment for patients with MDD across all subgroups examined here.

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