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Impact of sertraline daily treatment regimen on adherence, persistence and healthcare resource utilisation in patients with major depressive disorder or obsessive-compulsive disorder: A real-world evidence analysis from the United States

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Abstract

Objective: To generate real-world evidence (RWE) from the United States to assess the impact of pill burden and the importance of achieving a stable daily dose of sertraline (time taken, number of dose adjustments needed) on adherence/persistence and healthcare resource utilisation (HCRU).

Methods: Retrospective analysis of the PharMetrics® Plus database (1 October 2012 to 31 March 2020) in the United States. Eligible patients had major depressive disorder (MDD) or obsessive-compulsive disorder (OCD) and ≥1 claim for sertraline during index period (1 April 2013 to 31 March 2019, allowing 6-months prior, 1-year post-index follow-up). Patients who achieved stable daily dose of sertraline (>90 days on same dose) were categorised into five cohorts, depending on pill burden/daily dose: Cohort (1): 1 × 50 mg/d; Cohort (2): 1 × 100 mg/d; Cohort (3): 2 × 50 mg/d; Cohort (4): 1.5 × 100 mg/d; Cohort (5): 3 × 50 mg/d. Impact of pill burden on adherence/persistence and HCRU was assessed among cohorts using logistic regression analysis, and between patients who did vs did not stabilise on therapy. $P < .05$ was considered significant for all analyses.

Results: Of 224 412 eligible patients, 108 729 stabilised on sertraline (50, 100 or 150 mg/d) and formed Cohorts 1-5. Stabilised patients on lower pill burden had statistically higher adherence and were more likely to remain persistent throughout 1-year post-index period vs patients on higher pill burden but same overall dose (100 mg/d [Cohort 2 vs 3] and 150 mg/d [Cohort 4 vs 5], respectively). Patients who did not stabilise had significantly lower adherence/persistence vs patients who achieved stable daily dose (Cohorts 1-5 combined). Persistence improved when stable daily dose was achieved quickly (within 1-4 months) and efficiently (within 1-3 dose

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adjustments). Probability of HCRU increased for patients who did not stabilise on their initial prescription.

Conclusion: Simplifying treatment regimen and decreasing pill burden improved adherence and/or persistence with sertraline therapy (100 or 150 mg/d). Patients achieving stable daily dose of sertraline in an efficient and timely manner were more likely to remain persistent throughout 1-year follow-up.

1 | INTRODUCTION

Major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) are two common mood disorders affecting millions of individuals worldwide.[1,2] For example, in the United States, an estimated 17.3 million adults have had at least one major depressive episode, which represents at least 7.1% of all US adults.[3,4] Furthermore, a nationally representative sample (2005-2016) suggests an increasing trend for depression in US adults.[5] The prevalence of MDD is lower across China, but MDD is still the most prevalent mood disorder with a lifetime prevalence of 3.4% (across 31 provinces), and 12-month prevalence of 2.1%.[6] OCD is less common than MDD with a worldwide lifetime prevalence of ~1.3% (up to 2017).[2] OCD affects an estimated 2.2 million US adults, with a lifetime prevalence similar to that seen worldwide (1.2% of the US population).[7] OCD is more common in China than in the United States, with a lifetime prevalence double that seen in the US (~2.4%),[6] although the 12-month prevalence is similar to that seen worldwide (1.6%[6] vs 1.3%[2]). More nuanced findings can be seen when data are evaluated by age.[8-10] For example, in China, a lower overall prevalence is seen for those aged 15-59 years (0.10% in 2003[9]), while in secondary school students (mean age 14.7 years) and undergraduate students (mean age 21.3 years), the prevalence of OCD is higher, at 13.6%[8] and 17.1%,[10] respectively. These observations reflect other reports that suggest OCD frequently manifests in childhood,[11-13] and can negatively impact many aspects of daily life, including educational performance.[14] Although the reasons between the differences in prevalence reported in the United States and China are unknown, both OCD and MDD place a real burden on public health services around the world, and are leading causes of disability.[1,15]

Along with evidence-based talk therapies, professional guidelines recommend first-line antidepressant medications (ADMs) (eg, selective serotonin reuptake inhibitors [SSRIs] and serotonin–norepinephrine reuptake inhibitors [SNRIs]) as an initial treatment options for mood disorders.[16,17] Despite the availability of multiple ADMs, at least 30%-40% of patients fail to adequately respond to initial pharmacotherapy,[18] and 50%-60% of patients prematurely discontinue treatment.[19,20] Nonadherence and poor persistence with ADMs are recognised as key causes of treatment failure in mood disorders.[20,21] Nonadherence is particularly common in Chinese populations, where stigmatisation around depression and mood disorders often results in discontinuation of ADMs.[22,23]

What's known

- Obsessive-compulsive disorder and major depressive disorder place a large burden on health services and are leading causes of disability.
- Nonadherence and poor persistence are widely recognised as key causes of treatment failure in mood disorders.
- However, no data are available that discuss the influence of daily treatment regimen on adherence/persistence with sertraline in patients with these mood disorders, and moreover, if persistence then impacts healthcare resource utilisation (HCRU).

What's new

- This retrospective analysis of 224 412 patients from the PharMetrics®-Plus database (1 October 2012 to 31 March 2020), investigates the impact of sertraline pill regimen on adherence/persistence.
- Lower pill burden improved adherence and/or persistence with sertraline.
- Patients achieving a stable daily dose of sertraline in an efficient and timely manner were more likely to remain persistent during follow-up.
- Probability of HCRU increased for patients not stabilising on their initial prescription or taking up to 4 months to stabilise.

Sertraline is a first-line SSRI approved for the management of MDD and OCD in many countries, including China, and has a well-established safety and efficacy profile in different patient populations.[24,25] Sertraline was first approved in mainland China in the 1990s, but only the 50-mg formulation was approved up until 2020.[25] By contrast, 50- and 100-mg sertraline tablet formulations are widely used in many other countries and regions. However, no data are available that discuss the influence of daily treatment regimen on adherence and persistence with sertraline, and moreover, if persistence then impacts healthcare resource utilisation (HCRU). This study investigates the impact of sertraline daily pill burden on adherence, persistence and probability of remaining persistent with sertraline treatment through an analysis of real-world evidence

(RWE) from a diverse population of US patients with MDD or OCD. With limited data available from China, US data were used to represent prescribing trends in a large, diverse patient population. The impact of sertraline daily treatment regimen, timing of dose escalation, and final sertraline treatment regimen prescribed on persistence and HCRU are also assessed. We also investigate the impact of pill burden on drug treatment for MDD and OCD.

2 | METHODS

2.1 | Study design

This retrospective cohort analysis of the IQVIA PharMetrics® Plus claims database extended from 1 October 2012 to 31 March 2020. The IQVIA PharMetrics® Plus database is a patient-centric, closed claims database of fully adjudicated pharmacy, hospital and medical claims anonymised at the patient level, which captures the complete patient journey for all services billed to and covered by the patient's health plan.[26] The database includes data from commercial insurance, Medicare Advantage, managed Medicaid, self-insured and pharmacy-only plans. Available information includes demographic characteristics (eg age, sex and insurance plan and product type), inpatient and outpatient diagnoses and procedures and pre-rebate costs paid by health plans to providers.[26] The dataset is statistically de-identified, consistent with the Health Insurance Portability and Accountability Act. No direct subject contact occurred; therefore, informed consent, ethics committee approval and institutional review board approval were neither required nor sought.

2.2 | Study population

Eligible patients were any age with an International Classification of Diseases, Clinical Modification (ICD-CM), in both ICD-9-CM and ICD-10-CM versions, diagnosis code for MDD or OCD, and ≥1 prescription(s) for sertraline during the selection window (1 April 2013 to 31 March 2019). The selection window allowed for continuous enrolment during the 6-month pre-index period and the 1-year post-index period. The index date was defined as the date when sertraline therapy became stabilised, defined as >90 days on the same dose of sertraline after the initial prescription.

2.3 | Study cohorts

Daily dose and number of pills were collected within the prescribing data and were used to allocate patients into cohorts. Eligible patients were categorised into five cohorts based on stable daily dose of sertraline (index date) and prescription pill regimen:

- Cohort 1: patients taking 1 × 50-mg sertraline tablet (total daily dose 50 mg);
- Cohort 2: patients taking 1 × 100-mg tablet (total daily dose, 100 mg);
- Cohort 3: patients taking 2 × 50-mg tablets (total daily dose, 100 mg);
- Cohort 4: patients taking 1.5 × 100-mg tablets (total daily dose 150 mg);
- Cohort 5: patients taking 3 × 50-mg tablets (total daily dose, 150 mg).

Patients in the same sertraline stable daily dose cohort but with different pill regimen (based on dosage and quantity of tablets) were compared to understand the impact of pill burden on adherence, persistence and HCRU in the post-index period (Cohort 2 vs Cohort 3; Cohort 4 vs Cohort 5). Patients had to remain on the specific pill ratio to be within a given cohort. Patients who changed from their sertraline dose would not have been counted in a given cohort unless they remained on the stable daily dose for at least 90 days (index date). Within each cohort, time on stable daily dose of sertraline was calculated up to the point at which the patient changed their daily dose. Adherence, persistence and HCRU were assessed within each cohort.

Patients in Cohorts 1-5 achieved a stable daily dose at some point during the post-index period and were combined to form the 'achieved stable daily dose' group. Patients from the entire population who did not achieve a stable daily dose during the post-index period (ie, did not remain on a dose of sertraline for at least 90 continuous days) combined to form the 'did not achieve stable daily dose' group. These two groups of patients were compared to understand the impact of achieving a stable daily dose on adherence and persistence in the 1-year post-index period. Patients who did not achieve a stable daily dose did not have an 'index date' as defined for the other adherence analyses. Instead, the 'start date' was taken as the date of first sertraline prescription.

2.4 | Adherence and persistence

Patient adherence and persistence with sertraline were analysed over a 1-year post-index period in all patient cohorts.

Adherence was measured using the medication possession ratio (MPR), calculated as follows:

- MPR = [(days with drug on-hand without removing overlap during 360-day period)/360] × 100%.

Persistence was measured by time to discontinuation and a full year's persistence during the 1-year post-index period, defined as follows:

- Time to discontinuation = consecutive days from treatment initiation until discontinuation or end of the 1-year post-index period, whichever occurred first.
- Discontinuation was defined as a gap in index therapy ≥1.5 × days of the index therapy supply of the prior fill (discontinuation date

defined as last day of supply prior to gap).

2.5 | Healthcare resource utilisation

HCRU was defined as any disease-specific hospitalisation, physician office visit, emergency room (ER) visit, lab/pathology test, radiology exam, surgical service or other relevant outpatient ancillary services.

2.6 | Statistical analysis

Descriptive statistics were performed. For continuous variables, mean and standard deviation (SD) were computed. For categorical variables, counts and percentages were computed. Missing data were not imputed.

Multivariate logistic regression analysis was carried out to determine the impact of pill burden on the binary outcome variables, including the odds of a full year's persistence (yes/no), and the odds of any HCRU (yes/no) in the 1-year post-index period. Patients in the same sertraline stable daily dose cohort but with different pill regimen were compared (Cohort 2 vs Cohort 3; Cohort 4 vs Cohort 5). The impact of multiple covariates, including sex, age, region, payer type, and diagnosing physician, were assessed on the odds of persistence and disease-specific HCRU in the 1-year post-index period. A stepwise model-building approach was taken, with $P < .10$ for inclusion and retention of colinear variables. A Kaplan–Meier survival analysis was also carried out to determine the probability of a full year's persistence in the 1-year post-index period for patients on different pill burdens but the same daily dose (Cohort 2 vs Cohort 3; Cohort 4 vs Cohort 5).

Multivariate regression analysis was also carried out to determine the impact of achieving a stable daily dose, time taken to achieve dose stabilisation, and the number of dose changes (dose adjustments) prior to achieving a stable daily dose for patients on the odds of having a full year's persistence (yes/no), and the odds of having any disease-specific HCRU in the 1-year post-index period (yes/no) for all patients who achieved stable daily dose (Cohorts 1-5, combined). Impact of multiple covariates was assessed on the continuous/ordinal outcome variables, including time to achieve dose stabilisation (defined as >90 days on the same dose of sertraline therapy [reference: prescription date]), number of dose adjustments prior to achieving a stable daily dose (reference: no dose adjustments), and study cohort (reference: Cohort 1), along with other covariates listed above. A stepwise model-building approach was taken, with $P < .10$ for inclusion and retention of colinear variables. Odds ratios (ORs) were generated alongside 95% CI for all logistic regression analyses. A Kaplan–Meier survival analysis was also carried out to determine the probability of a full year's persistence in the 1-year post-index period for patients who achieved stable daily dose (Cohorts 1-5, combined) compared with those who did not achieve stable daily dose, but filled their prescriptions at least twice. Two-sided P value of $< .05$ was considered statistically significant for all analyses.

3 | RESULTS

3.1 | Study cohorts

Nearly three million patients were prescribed at least one dose of sertraline during the study window (n = 2 969 016). Of these, 224 412 patients with a diagnosis of MDD or OCD were eligible for inclusion (Figure 1). In total, 108 729 patients achieved a stable daily dose within the selection window, and these patients were allocated to one of the five mutually-exclusive cohorts (Cohorts 1-5), depending on daily dose and prescription regimen, as outlined in Table S1. The majority of patients across Cohorts 1-5 were female (64.4%-69.8%). Mean (±SD) age for patients who achieved stable daily dose (Cohorts 1-5, combined) was 36.6 (±16.0) years and was lower for patients who did not achieve stable daily dose (33.7 ± 15.6 years) (Table 1). Depression, hypertension, dyslipidaemia and generalised anxiety disorder (GAD) were common comorbidities across cohorts (Table 1). Half of patients who achieved stable daily dose (47% [n = 50 617/108 729]) changed their sertraline dose at least once prior to achieving a stable daily dose in the 1-year post-index period, and 48% (n = 52 244/108 729) took ≥1 month to achieve a stable daily dose.

3.2 | Impact of pill burden on adherence and persistence with sertraline therapy in the 1-year post-index period

The majority of patients (95% [n = 37 852/39 909]) on 100 mg as their stable daily dose (Cohorts 2 and 3) took the 100-mg tablet once-daily (Cohort 2). These patients in Cohort 2 (1 × 100 mg/d) had higher adherence (MPR) and better persistence across all measures when compared with patients on the same dose (100 mg/d) but on a higher pill burden (Cohort 3, 2 × 50 mg/d) (Table 2). The majority of patients (90% [n = 8577/9536]) on 150 mg as their stable daily dose (Cohorts 4 and 5) took 1.5 × 100 mg/d once daily (Cohort 4). These patients in Cohort 4 (1.5 × 100 mg/d) had higher adherence (MPR) compared with patients on the same dose (150 mg/d) but on a higher pill burden (Cohort 5, 3 × 50 mg/d) (MPR 76% vs 74%; $P = .023$; Table 2). In the Kaplan–Meier survival analyses, patients who achieved a stable daily dose and on a lower pill burden were more likely to remain persistent in the 1-year post-index period compared with patients on a higher pill burden, regardless of treatment regimen (Figure 2).

3.3 | Impact of pill burden on probability of remaining persistent with sertraline therapy and probability of HCRU in the 1-year post-index period

In a stepwise logistic regression analysis, higher pill burden was associated with lower odds of being persistent with sertraline therapy in the 1-year post-index period for patients on 100-mg sertraline as their stable daily dose (Cohort 3 vs Cohort 2; OR: 0.82 [95% CI: 0.75-0.89]; $P < .0001$) but did not reach significance for patients on stable

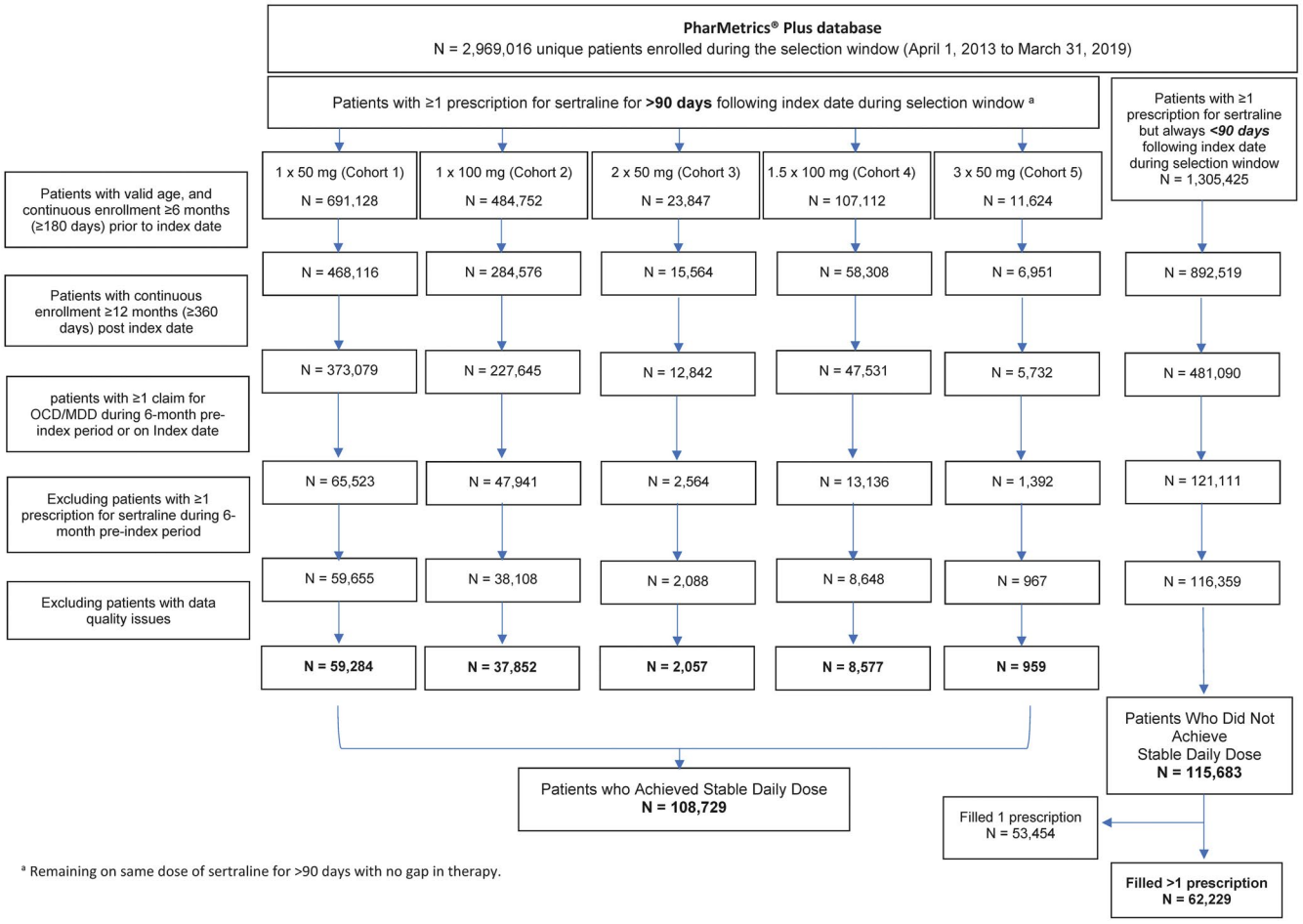


FIGURE 1 Patient disposition through the trial and allocation to cohorts, based on sertraline treatment regimen and achieving a stable daily dose

dose of 150-mg sertraline (Cohort 5 vs Cohort 4; OR: 0.89 [95% CI: 0.78-1.02]; $P = .097$) (Figure 3). Significant variables that positively impacted likelihood of remaining persistent in the pill-burden analysis included older age (≥45 vs <45 years) or being female (Figure 3).

Higher pill burden was not associated with increased HCRU in the 1-year post-index period, regardless of treatment regimen (Figure S1). Being diagnosed by a psychiatrist (vs primary care physician [PCP]) was a positive predictor of HCRU in the 1-year post-index period, regardless of sertraline dose (Figure S1). Conversely, being diagnosed by all other types of healthcare provider was associated with a lower likelihood of HCRU in the 1-year post-index period, regardless of sertraline dose (Figure S1).

3.4 | Impact of achieving stable daily dose on measures of adherence and persistence

Patients who did not achieve stable daily dose had significantly lower MPR and persistence across all measures compared with patients who achieved stable daily dose (Cohorts 1-5 combined) in the 1-year post-index period (Table 2). Overall, 60% of patients who achieved stable daily dose had a full year's persistence with sertraline therapy compared with just 5% of patients who did not achieve stable daily dose (MPR 60.0% vs 4.9%; $P < .0001$; Table 2). For patients who did not achieve stable daily dose despite receiving more than one prescription, 81% were prescribed ≤50-mg sertraline as their initial prescription (Figure S2).

Time taken and number of dose adjustments to achieve a stable daily dose were two key variables impacting adherence and persistence with sertraline therapy. For patients who achieved stable daily dose, MPR and time to discontinuation increased when patients undertook more dose adjustments to stabilise their daily dose (Figure 4A). MPR and persistence also generally increased with greater number of months taken to achieve a stable daily dose of sertraline (Figure 4B).

Based on the stepwise logistic regression analysis, patients titrating to a stable daily dose in an efficient (ie, <4-dose changes) and timely (ie, within 4 months) manner, and for patients who did not stay at their initial dose of sertraline, had a significantly higher likelihood of being persistent in the 1-year post-index period (Figure 5). Other variables that significantly increased odds of persistence in 1-year post-index period were older age (≥45 vs <45 years), being female

TABLE 1 Demographics, comorbidities and concomitant medication use at index date by study cohort

	Total stable daily dose of sertraline					
	50 mg/d	100 mg/d		150 mg/d		
	Cohort 1 (1 × 50 mg) (n = 59 284)	Cohort 2 (1 × 100 mg) (n = 37 852)	Cohort 3 (2 × 50 mg) (n = 2057)	Cohort 4 (1.5 × 100 mg) (n = 8577)	Cohort 5 (3 × 50 mg) (n = 959)	Did not achieve stable daily dose[a] (N = 115 683)
Female, n (%)	41 379 (69.8)	25 183 (66.5)	1421 (69.1)	5731 (66.8)	614 (64.0)	77 452 (67.0)
Age, mean ± SD	36.5 ± 16.1	36.6 ± 15.8	39.3 ± 16.7	36.0 ± 15.8	35.4 ± 16.1	33.7 ± 15.6
Comorbidities, n (%)[a]						
Alcohol/drug abuse	3664 (6.2)	3346 (8.8)	129 (6.3)	793 (9.2)	95 (9.9)	11 844 (10.2)
Depression	34 441 (58.1)	25 552 (67.5)	1303 (63.3)	6480 (75.6)	715 (74.6)	73 587 (63.6)
Dyslipidaemia	8068 (13.6)	5376 (14.2)	334 (16.2)	1229 (14.3)	128 (13.3)	12 340 (10.7)
Hypertension	9850 (16.6)	6536 (17.3)	366 (17.8)	1414 (16.5)	131 (13.7)	15 980 (13.8)
Sleep disorders	6716 (11.3)	5214 (13.8)	313 (15.2)	1307 (15.2)	142 (14.8)	14 010 (12.1)
Smoking	5317 (9.0)	3830 (10.1)	192 (9.3)	778 (9.1)	88 (9.2)	13 494 (11.7)
GAD	9021 (15.2)	7506 (19.8)	361 (17.5)	2267 (26.4)	237 (24.7)	21 395 (18.5)
CCI, mean ± SD	0.3 ± 1.0	0.3 ± 0.9	0.3 ± 1.1	0.2 ± 0.7	0.2 ± 0.9	0.2 ± 0.9
Concomitant medications of interest, n (%)						
Citalopram	3139 (5.3)	2852 (7.5)	160 (7.8)	766 (8.9)	84 (8.8)	6345 (5.5)
Escitalopram	4270 (7.2)	3735 (9.9)	188 (9.1)	1063 (12.4)	118 (12.3)	9843 (8.5)
Fluoxetine	3636 (6.1)	3387 (8.9)	182 (8.8)	950 (11.1)	104 (10.8)	8919 (7.7)
Fluvoxamine	130 (0.2)	186 (0.5)	21 (1.0)	77 (0.9)	8 (0.8)	420 (0.4)
Paroxetine	1053 (1.8)	887 (2.3)	43 (2.1)	225 (2.6)	26 (2.7)	2397 (2.1)
Vilazodone	236 (0.4)	251 (0.7)	16 (0.8)	110 (1.3)	10 (1.0)	440 (0.4)

Abbreviations: CCI, Charlson Comorbidity Index; GAD, generalised anxiety disorder; SD, standard deviation.

[a]Patients who did not stabilise after filling ≥1 prescription.

(vs male), and being diagnosed by a psychologist (vs PCP), based on either number of dose adjustments or time taken to achieve a stable daily dose (Figure 5). In a Kaplan–Meier survival analysis, patients who did not stabilise on sertraline therapy, but filled their prescriptions at least twice, were less likely to be persistent over the 1-year follow-up period vs patients who achieved a stable daily dose (Figure S3).

3.5 | Impact of time taken and number of changes in dose prior to dose stabilisation on HCRU in the 1-year post-index period

The probability of HCRU in the 1-year post-index period increased for patients who did not stabilise immediately on their initial sertraline therapy (based on dose adjustments or time to achieve stable daily dose) (Figure S4). Stabilised patients incurred a range of disease-specific doctor's visits and diagnostic tests throughout the post-index period (Table S2). The largest number of claims was seen for physician office visits in the 1-year post-index period (Table S2). More specifically, the probability of HCRU significantly increased in the post-index period for patients who took up to 4 months to stabilise on sertraline therapy (Figure S4). Other variables that increased odds of HCRU included being diagnosed by a psychiatrist compared with a PCP (OR: 1.24 [95% CI: 1.16-1.32]; $P < .0001$; Figure S4).

4 | DISCUSSION

This analysis of 224 412 patients with MDD or OCD indicates that prescribing regimen and path to achieving a stable daily dose of sertraline therapy impact the likelihood of remaining persistent with a therapy regimen, regardless of sertraline dose (100 or 150 mg/d). Specifically, patients titrating to a stable daily dose of sertraline in an efficient and timely manner were more likely to remain persistent for the 1-year post-index period compared with patients who took longer and/or required more dose adjustments to stabilise on sertraline therapy. Patients on a higher pill burden were also less likely to be persistent with therapy, compared with patients on less pills but the same overall dose. Given the importance of adherence and persistence for long-term management of mental health conditions,[16,19] these observations suggest that physicians should ensure patients achieve an effective stable dose of sertraline efficiently, using the most simplified pill regimen possible.

TABLE 2 Measures of adherence (based on MPR) and persistence with sertraline therapy

	Cohort 1 (1 × 50 mg) (n = 59 284)	Cohort 2 (1 × 100 mg) (n = 37 852)	Cohort 3 (2 × 50 mg) (n = 2057)	Cohort 4 (1.5 × 100 mg) (n = 8577)	Cohort 5 (3 × 50 mg) (n = 959)	Achieved stable daily dose (N = 108 729)	Did not achieve stable daily dose[d] (N = 62 229)
Adherence							
MPR (%)	73	75	73[a]	76	74[b]	77	31[e]
Persistence							
Full 1-year's persistence (%)	56.2	59.7	55.4[a]	59.8	56.6	60.0	4.9[e]
Number of days continually persistent (including pts with full 1-year's persistence)	271.7	281.3	271.3[a]	284.2	273.7[c]	279.2	102.5[e]

Note: Start date for these adherence comparisons was date of first sertraline prescription as patients who did not achieve a stable daily dose did not have an 'index date' as defined for the other adherence analyses. Independent comparisons conducted using parametric *t* test or chi-square test or Fisher's exact test for categorical variables.

[a]$P \leq .0001$ vs Cohort 2.

[b]$P = .0225$ vs Cohort 4.

[c]$P = .0058$ vs Cohort 4.

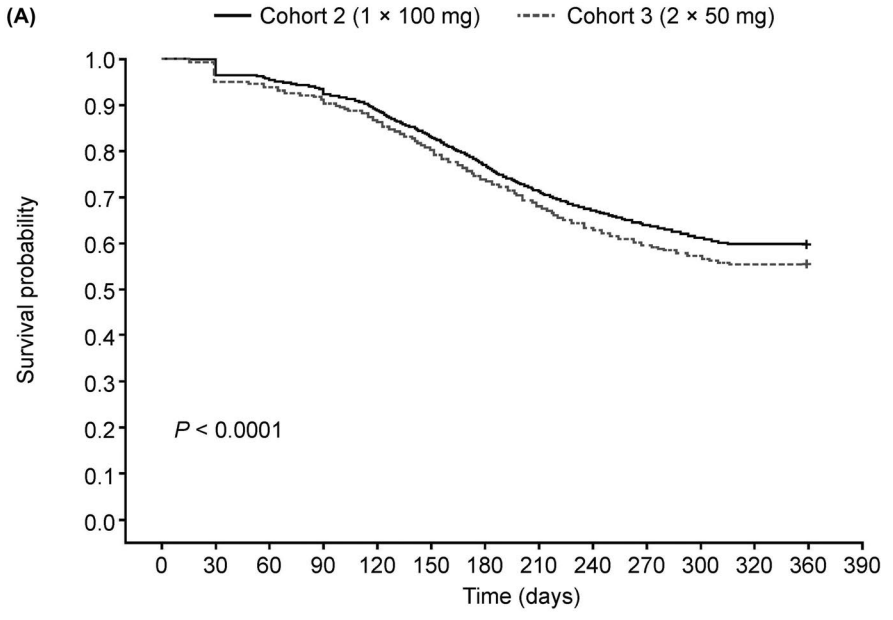
[d]Patients who did not stabilise after filling >1 prescription (ie, filled their prescription at least twice).

[e]$P < .0001$ vs cohort achieved stable daily dose (Cohorts 1-5 combined).

OCD and MDD are highly prevalent mood disorders in both the United States and China,[2-7] and nonadherence is a particular problem in Chinese patients.[22,23] With limited data available from China, it is useful to study prescribing practices from other countries where large data repositories are available, in order to provide learnings for physicians in China and internationally. Our study highlights a number of learnings for these physicians. Firstly, simplifying a patient's treatment regimen (ie, from two pills to one or three pills to two) generally improved adherence and/or persistence with sertraline but did not significantly impact HCRU. Adherence is a multifaceted issue,[27] with pill burden a key factor.[21] For example, in bipolar disease, pill burden is associated with dose irregularity, a proxy measure of adherence.[28] Of patients treated with sertraline, the majority were on a one-tablet regimen (ie, 1 × 100 mg/d), suggesting physicians favoured the single-tablet regimen and did not prescribe multiple pills as standard practice, in line with guidelines recommending that treatment regimens should be simplified.[29]

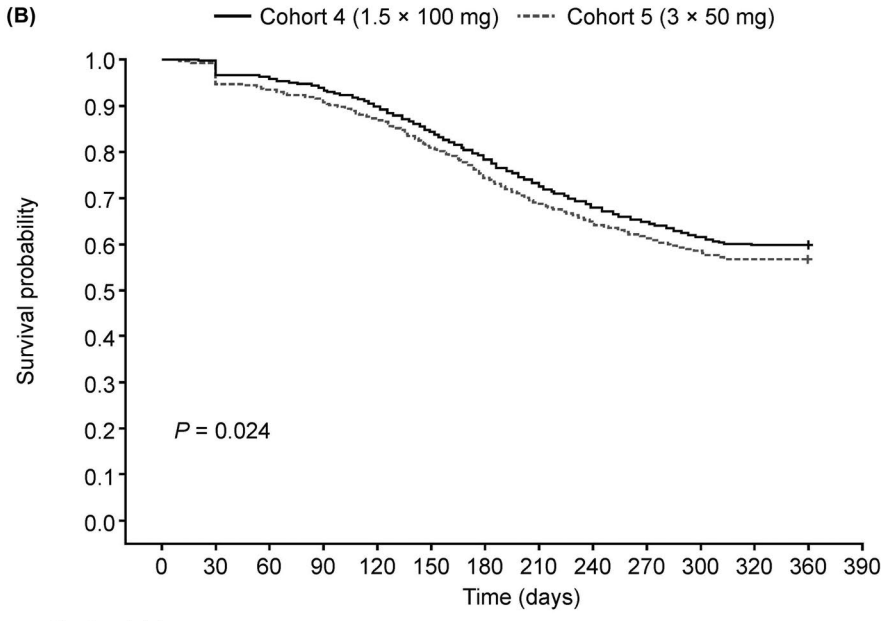
Achieving a stable daily dose of sertraline was a key variable impacting medication adherence and persistence throughout the 1-year follow-up period, in this study of US claims data. However, the path to a stable daily dose was varied. International guidelines suggest physicians follow a structured titration approach to ensure patients achieve an appropriate therapeutic dose, with a reasonable titration plan and simplified dosing regimen.[29] Despite this guidance, there is usually no clear timeline suggested, with physicians adopting a titration tempo based on their individual patient/preferences or local guidelines/practices, and variable follow-up schedules. Early adherence with ADMs is key for successful management of depression, as up to 60% of patients may discontinue ADMs within the first 3 months of treatment.[19,20,30] To optimise patient's persistence, we found that physicians need to focus on titrating patients in a timely manner but to ultimately ensure they achieve a stable daily dose of sertraline. Taking longer than 4 months to stabilise negatively impacted 1-year persistence, as did undertaking ≥4 dose adjustments prior to achieving a stable daily dose. These observations are in-line with a previous study in patients with depression, reporting that dose and switching therapy negatively impacted long-term persistence.[31] Patients may become unsettled by too many medication adjustments and not having a clear titration schedule, and these may negatively impact persistence. ADMs are commonly associated with a lag to treatment onset, and this impacts patients' perception of therapy effectiveness during early treatment.[32] Collectively, our observations help to highlight the importance of treatment optimization and early monitoring to ensure patients are not kept on an ineffective initial prescription but titrated to a stable regimen. Additional research is required to better understand the impact of different treatment regimens (based on timing and dose adjustments) and, moreover, patient or prescriber characteristics that lead to patients achieving a stable daily dose of sertraline.

Interestingly, the type of healthcare provider making the initial diagnosis had a significant impact on the likelihood of persistence and on HCRU in the 1-year post-index period, where for example, patients diagnosed by a psychiatrist had higher HCRU vs other types



Number at risk

Cohort 2	37852	37810	36141	35278	33630	31460	29098	26957	25379	24194	23157	22599	22581	0
Cohort 3	2057	2044	1930	1885	1786	1655	1519	1404	1300	1230	1175	1140	1140	0

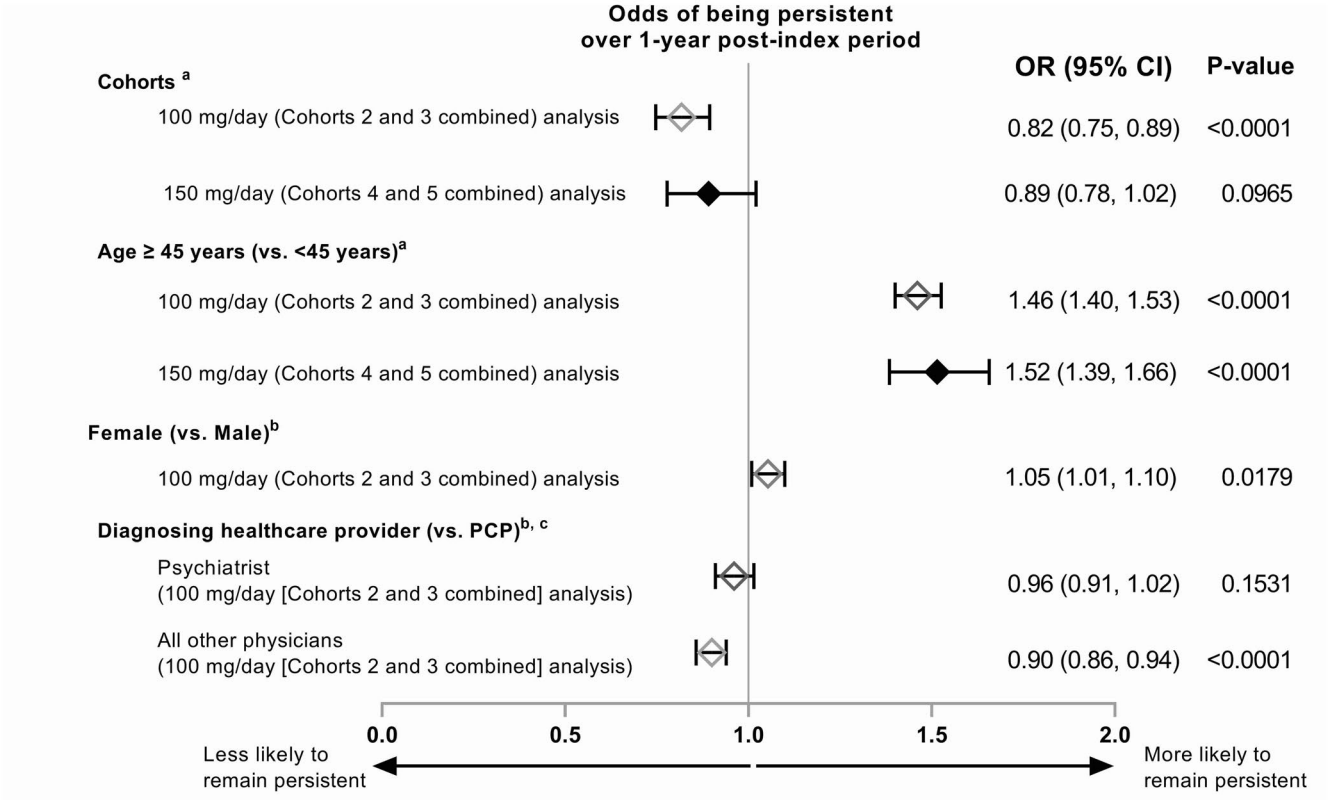


Number at risk

Cohort 4	8577	8560	8228	8052	7718	7241	6746	6253	5854	5549	5274	5131	5127	0
Cohort 5	959	950	897	875	835	777	714	662	621	589	560	544	543	0

FIGURE 2 Kaplan–Meier survival curves for probability of remaining persistent with sertraline during the 1-y post-index period for patients who achieved stable daily dose on different pill regimens (A) Cohort 2 (1 × 100 mg) vs Cohort 3 (2 × 50 mg); (B) Cohort 4 (1.5 × 100 mg) vs Cohort 5 (3 × 50 mg)

of provider. Although we do not capture reasoning, it could be that psychiatrists are scheduling more regular appointments with their patients, possibly reflecting their specialty in treating more severe patients who require close monitoring (although severity of disease was not captured). Physicians should take every opportunity to monitor patients' adherence and ensure they receive an adequate dose of ADM to manage their underlying mood disorder.[17,29,33] Any healthcare provider contact allows time to discuss adherence, and

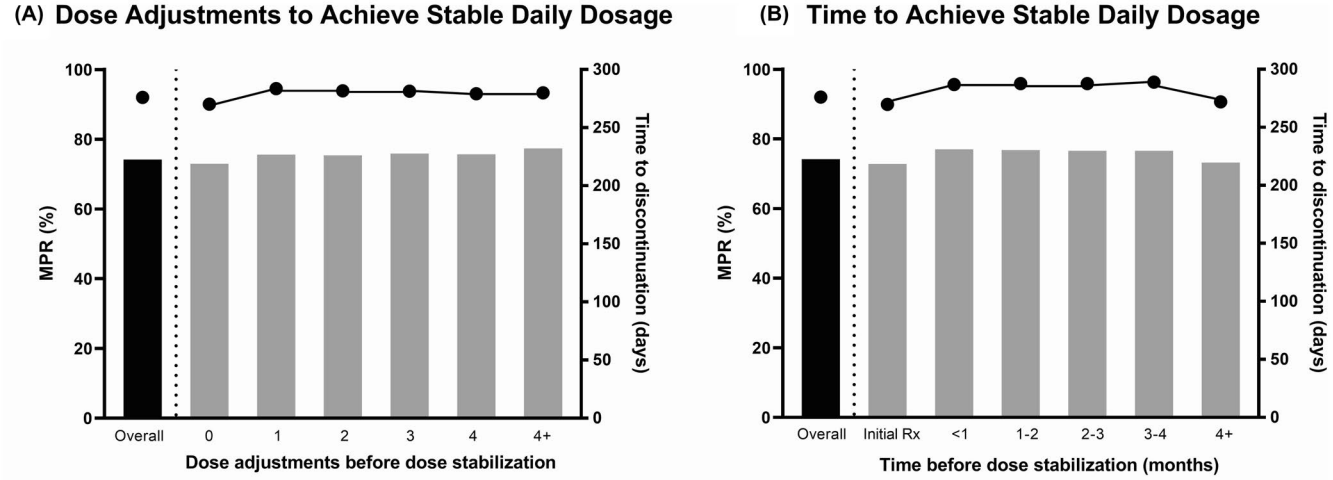


Cohort 1 = 1 × 50 mg; Cohort 2 = 1 × 100 mg; Cohort 3 = 2 × 50 mg; Cohort 4 = 1.5 × 100 mg; Cohort 5= 3 × 50 mg.
Abbreviations: CI, confidence interval; OR, odds ratio; PCP, primary care physician.
[a] Non-filled points: for the 100 mg/day (Cohorts 2 and 3 combined) analysis; filled points: for the 150 mg/day (Cohorts 4 and 5 combined) analysis.
Stepwise model-building approach (P < 0.10 for inclusion and retention) was taken.
[b] In the 150 mg/day (Cohorts 4 and 5 combined) analysis: Model excluded gender and diagnosing healthcare provider at index due to mixed stepwise selection.
[c] In the 100 mg/day (Cohorts 2 and 3 combined) analysis: Model excluded psychologist due to mixed stepwise selection.

FIGURE 3 Multivariate, logistic regression analysis for odds of full 1-year's persistence with sertraline therapy for patients in Cohort 2 (1 × 100 mg) vs Cohort 3 (2 × 50 mg) or Cohort 4 (1.5 × 100 mg) vs Cohort 5 (3 × 50 mg) (pill burden analysis)

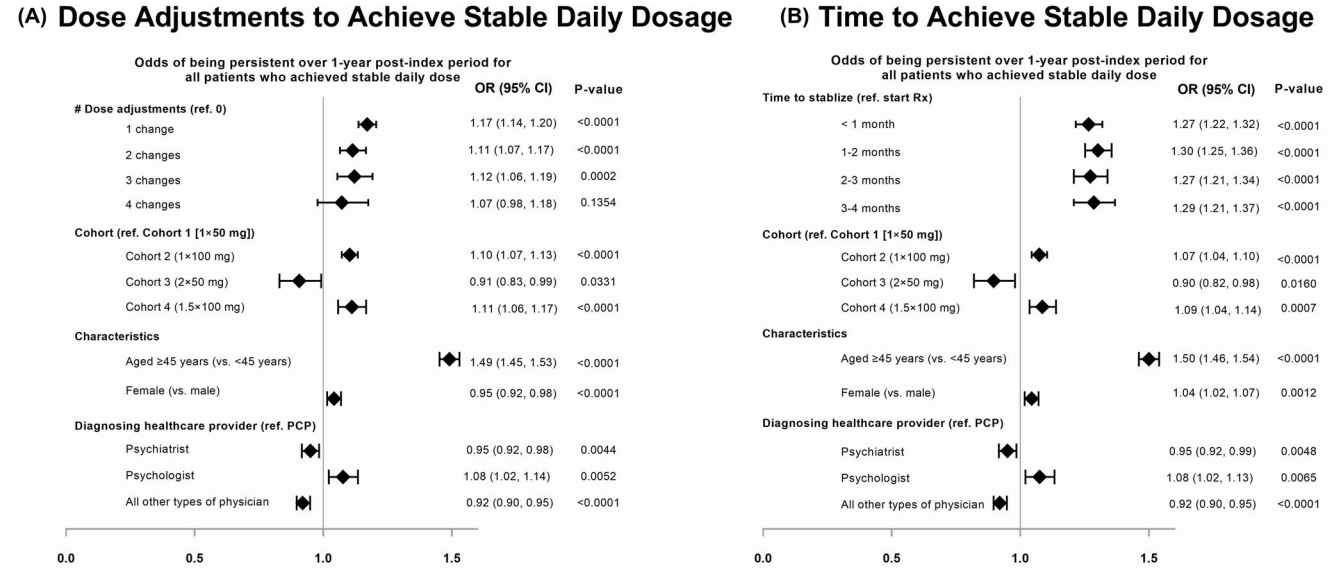
outline a titration schedule. Patients' attitudes and beliefs are known to impact adherence.[34] For example, studies in China report patients' misconceptions about ADMs,[35,36] with key reasons for nonadherence including concerns about long-term side effects, perceived lack of benefit, and believing themselves cured by treatment already received.[35] As noted above, the lag to treatment onset experienced with ADM treatment impacts patients' perception of effectiveness during early treatment.[32] Although underlying reasons for nonadherence are not captured in our study, we provide new insights into the importance of achieving a stable daily dose of sertraline and moreover help to provide context around the negative impact high pill burden, time taken and number of dose adjustments undertaken have on persistence. These observations may help healthcare providers produce a more structured titration plan for patients initiating sertraline therapy.

There are potential limitations of using retrospective data to generate RWE. Claims data are typically collected for billing purposes, and the present database of US managed care enrolees represents patients with access to a healthcare plan or able to self-insure. Although our study represents a broad range of patients treated with sertraline for MDD or OCD, wider generalizability to other populations and other countries outside the United States, such as China, is unknown, and would require specific study. Our study cohort included patients treated for either MDD or OCD, although each condition would have been managed differently, based on best clinical judgement, which would vary depending on severity of disease. The maximum dose of sertraline is the same for both conditions (200 mg/d), and initial dose is similar (50 mg/d), except for OCD patients 6-12 years of age, where an initial dose of 25 mg/d is suggested.[24] How treatment regimen and time to dose stabilisation differs for OCD or MDD patients separately was not investigated in the present analysis. Although we highlight that older age (≥45 years) impacted the likelihood of persistence, patients in the database were primarily working age (mean age ~35 years), and only 5% were ≥65 years. Prescribing information suggests that dose selection for elderly patients should be conservative, starting low to reflect the greater frequency of hepatic, renal or cardiac issues and other concomitant diseases or concomitant therapies.[24] Different



Bars represent adherence (% medication possession ratio [MPR]); line graph represents persistence (number of days to discontinuation), including patients with full year's persistence.
Stable Daily Dose Cohort = Patients in Cohorts 1–5 who achieved a stable daily dose (n = 108,729).

FIGURE 4 Impact of (A) number of dose adjustments prior to achieving a stable daily dose and (B) time taken to achieve a stable daily dose of sertraline on adherence (MPR) and number of days remaining persistent (time to discontinuation)



Abbreviations: CI, confidence interval; OR, odds ratio; PCP, primary care physician.
Cohort 1 = 1 × 50 mg; Cohort 2 = 1 × 100 mg; Cohort 3 = 2 × 50 mg; Cohort 4 = 1.5 × 100 mg; Cohort 5= 3 × 50 mg.
Stepwise model-building approach (P < 0.10 for inclusion and retention) taken. (A) Dose adjustment analysis: Model excluded 4+ changes and Cohort 5 (150 mg, 3 × 50 mg). (B) Time to stabilization analysis: Model excluded 4+ months and Cohort 5 (150 mg, 3 × 50 mg).

FIGURE 5 Multivariate, logistic regression analysis for odds of full 1-year's persistence with therapy for all patients who achieved a stable daily dose according to (A) number of dose adjustments prior to achieving a stable daily dose and (B) time taken to achieve a stable daily dose, of sertraline

observations may have been found in a cohort of predominately elderly patients. The impact of concomitant medications on overall pill burden, adherence and persistence is also unknown. Although higher sertraline pill burden was found to negatively impact adherence, physicians may have prescribed sertraline therapy as two vs one pill, for example, in order to limit a patient's fear around side effects,[30,35,37] when uptitrating to a higher dose. Present guidance encourages initiation of medication at a low initial dosage and then to titrate up to the appropriate daily dose, with a focus on minimising side effects.[16,24] Physicians should then simplify the regimen (ie, from 50 mg twice daily to 100 mg once daily) when patients stabilise, and not increase pill burden unless essential. These and other prescriber

variables would be present within the dataset and influence selection of dose regimen. Finally, time taken and number of dosage changes prior to achieving a stable daily dose had varying impacts on HCRU, and no clear conclusions could be drawn. Nevertheless, these data, representing a large, diverse cohort of US patients treated with sertraline for MDD or OCD support a simplified treatment regimen (ie, low pill-burden), where patients are uptitrated from their initial prescription and closely monitored to stabilise on an effective daily dose. Further research is needed to see how these US data reflect observations in other populations of patients with MDD and OCD, where different dose combinations may be available.

5 | CONCLUSION

This analysis of claims data representing a diverse population of patients with MDD or OCD from the United States demonstrates that a lower pill burden may help to improve adherence and/or persistence with sertraline therapy. Patients achieving a stable daily dose of sertraline in an efficient and timely manner were more likely to remain persistent during the 1-year follow-up period. These observations give an insight for prescribing physicians regarding how sertraline daily treatment regimen may impact adherence (based on MPR), persistence and HCRU.

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DISCLOSURES

G. Wang has no conflict of interest. T. Si has no conflict of interest. J. S. Imperato and E. A. Pappadopulos are former employees of Viatris (formerly Upjohn a division of Pfizer). LL Yang, KH Zou, YO Jin, L. Yan, JZ Li and W Yu are full-time employees of Viatris.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and implementation of the research presented and to the analysis and/or interpretation of the results. All authors provided critical review of the manuscript and approved the final content for submission. All authors are accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated. The study data will be provided for non-commercial use upon request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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