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Evaluating the efficacy of blister packaging in improving medication adherence within psychiatry: A systematic literature review

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Abstract

Introduction: Medication nonadherence is a prevalent and significant public health issue in the United States, particularly among patients with psychiatric disorders. Blister packaging medications is one of the most widely recognized and validated strategies for enhancing medication adherence. Given the paramount importance of adherence in psychiatry and the demonstrated effectiveness of blister packaging in chronic disorders, it is imperative to evaluate its effect in this context.

Methods: A systematic literature review was conducted in PubMed and Google Scholar in May 2024 to identify relevant studies assessing the effect of blister packaging on medication adherence, health outcomes, and health care costs in psychiatry. Studies were included if they provided quantitative data on the effects of blister packaging on medication adherence in psychiatry. A meta-analysis was not performed due to differences in definitions of adherence in the included studies.

Results: The review included 3 clinical studies and 1 cost-utility analysis (CUA). All 3 clinical studies demonstrated that blister packaging improved medication adherence rates. However, minimal data was available regarding its effect on clinical or patient-reported outcomes. The CUA found that blister packaging was dominant (less costly and more effective) compared with standard vial packaging.

Discussion: The evidence presented in this review substantiates the positive effect for blister packaging in a psychiatric population. Nevertheless, due to the limited scope and size of the studies reviewed, further research with larger sample sizes is needed to fully assess the broader effect of blister packaging on clinical outcomes and health care costs within psychiatry.

Keywords: behavioral health, mental health, blister packaging, medication adherence packaging, adherence, compliance, health outcomes

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Introduction

Medication nonadherence is a hidden epidemic in the United States across medication classes, disease states, and patient populations.[1] Patients with psychiatric disorders are particularly vulnerable to this issue. Studies indicate nonadherence rates in these patients range from 12% to 88%.[2-9] Nonadherence in psychiatric disorders can stem from several factors, including denial of the disorder,[8] psychiatric and cognitive factors,[3,8,10] unwillingness to use medication,[3] medication side effects,[3] complexity of medication regimen,[11,12] patient-provider relationship,[2,13] demographic variables,[2,14] and/or forgetfulness.[8,15] Patients nonadherent to their psychiatric medications face a significantly higher risk of disease-specific and all-cause hospitalization.[4,16-19] Nonadherence also correlates with worse overall clinical outcomes and increased health care costs[20] with 1 study finding patients nonadherent to noninjectable atypical antipsychotics having almost $20 000 more total health care costs annually compared with those who were adherent.[21] These findings hold true when both assessing dichotomous definitions of adherent versus nonadherent[21] as well as differing rates of adherence (ie, <25%, 25% to 49%, 50% to 74%, 75%+).[22]

Numerous strategies and initiatives aim to promote and improve medication adherence with separate initiatives attempting to target various root causes of the nonadherence.[23-25] These strategies include adherence packaging interventions such as blister packaging or pouch packing medications, alarm reminders, patient refill reminders, medication therapy management, and prescriber outreach or refill reminders. Each of these interventions shows various degrees of success in improving medication adherence.[23-35] To maximize success, multiple strategies and initiatives may be undertaken concurrently to increase the likelihood of patients becoming adherent to their medication regimens and, therefore, having higher chances of treatment success.[35]

Blister packaging medications is one of the most recognized and widely used medication adherence-enhancing initiatives, consistently demonstrating success in improving medication adherence for the last several decades across various patient populations.[23-25] In cardiovascular disorders, blister packaging for antihypertensives was found to significantly increase the percentage of patients deemed adherent (proportion of days covered ≥80%)[26] while also showing a significant reduction in diastolic and systolic blood pressure.[27,36,37] In a randomized controlled trial (RCT) of patients with diabetes, a significant reduction in HbA1c was seen 8 months postintervention for the patients receiving medication in blister packaging versus "usual containers" (−0.95 ± 0.22 versus −0.15 ± 0.25, P = .026).[38] Whereas blister packaging has effectively improved adherence in chronic maintenance medications, psychiatric medications present unique challenges due to diverse clinical and demographic factors that may lead to patients not starting or continuing their medications. Additionally, reasons for nonadherence for psychiatric disorders differ from those for cardiovascular and endocrinology diseases.[8-12] These challenges highlight the need for a thorough evaluation of blister packaging's effect specifically within the context of psychiatry. Therefore, a systematic literature review was conducted to evaluate the documented effect of blister packaging medications on medication adherence in psychiatry. This review aims to provide clearer insights and potentially inform future interventions to enhance adherence in this vulnerable population.

Methods

Search Strategy

A systematic literature review (SLR) was conducted in PubMed/Medline and Google Scholar in May 2024. This review aimed to identify the published literature assessing the effect of blister packaging medications in psychiatric settings and the effect on medication adherence, health outcomes, and health care costs. The search strategy is available in Table 1. The SLR was performed according to industry standards and best practices[39-41] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[42,43] A review of citations was also conducted to identify studies that may not have been indexed in the search databases but met the inclusion criteria.[44-47]

Study Selection

Studies were included if they were published in English and assessed the effect of blister packaging medications on medication adherence in psychiatric disorders. A wide array of psychiatric disorders was evaluated to be as inclusive as possible in assessing the potential effect. Published conference abstracts were included if the abstract contained enough information regarding the study methodology to determine if the interventions of interest in the studies were conducted appropriately and/or if there was a conference poster that went along with the published abstract that provided this information. Exclusion criteria consisted of studies that did not quantitatively assess the effect of blister packaging medications on medication adherence in psychiatric disorders, including editorials, letters to the editor, SLRs, and qualitative analyses. Whereas SLRs were not included in the review, SLRs identified during the search process were included in the full-text review of citations to identify additional studies that may have met the inclusion criteria but were not found in the original search. Additionally, if studies assessed the effect of blister packaging on medication adherence across multiple disorders or disease states, results would have to be stratified by patient subgroups to show the effect directly on those with psychiatric

TABLE 1: **Search strategies**

PubMed/Medline Search		
PubMed	**Search Terminology**	**Hits**
1	("Pill container" OR "Pill containers" OR "Medication Container" OR "Medication Containers" OR "Blister packing" OR "blister packaging" OR "blister-packing" OR "blister-packaging" OR "blister pack" OR "blister-pack" OR "calendar packing" OR "calendar packaging" OR "calendar-packing" OR "calendar-packaging" OR "calendar pack" OR "calendar-pack" OR "pouch packing" OR "pouch packaging" OR "pouch-packing" OR "pouch-packaging" OR "pouch pack" OR "pouch-pack" OR "booklet packing" OR "booklet packaging" OR "booklet-packing" OR "booklet-packaging" OR "booklet pack" OR "booklet-pack" OR "medication blister" OR "drug blister" OR "Unit-of-use" OR "Unit of use")	5664
2	("Depression" OR "antidepressants" OR "anti-depressants" OR "antidepressant" OR "anti-depressant" OR "behavioral health" OR "mental health" Or "anti-psychotics" OR "anti-psychotic" OR "antipsychotics" OR "antipsychotic" OR "major depressive disorder" OR "major-depressive-disorder" OR "MDD" OR "psychiatric" OR "psychology" OR "psychological" OR "schizophrenic" OR "schizophrenia" OR "bipolar" OR "anxiety" OR "obsessive compulsive disorder" OR "OCD" OR "anxiolytics" OR "mania" OR "panic disorder" OR "psychosis" OR "selective serotonin reuptake inhibitors" OR "selective serotonin reuptake inhibitor" OR "SSRI" OR "SSRIs" OR "serotonin and norepinephrine reuptake inhibitors" OR "serotonin and norepinephrine reuptake inhibitor" OR "serotonin-norepinephrine reuptake inhibitors" OR "serotonin-norepinephrine reuptake inhibitor" OR "SNRI" OR "TCA" OR "TCAs" OR "monoamine oxidase inhibitor" OR "monoamine oxidase inhibitors" OR "MAOI" OR "MAOIs" OR "benzodiazepines" OR "benzodiazepine" OR "Opioid use disorder" OR "OUD" OR "opioid-use disorder" OR "alcoholism" OR "alcohol use disorder" OR "AUD" OR "alcohol-use disorder" OR "MAT" OR "MOUD" OR "medication assisted therapy" OR "medication-assisted therapy" OR "Medications for opioid use disorder" OR "detoxification" OR "SUD" OR "substance use disorder")	2 892 974
3	("Adherent" OR "adherence" OR "nonadherent" OR "nonadherence" OR "compliance" OR "compliant" OR "noncompliance" OR "noncompliant" OR "persistent" OR "persistence" OR "nonpersistent" OR "nonpersistence")	877 283
4	1 AND 2 AND 3	74
Google Scholar Search		
Google Scholar	**Search Terminology**	**Hits**
1	"Pill container" OR "Blister packing" OR "blister pack" OR "calendar packing" OR "unit-of-use"	13 900
2	"behavioral health" OR "mental health" OR psychiatric OR schizophrenia OR depression OR anxiety	5 650 000
3	Adherent OR adherence OR nonadherent OR nonadherence	3 410 000
4	1 AND 2 AND 3	2210

disorders. After removing duplicates, a review of titles and then abstracts was conducted by 2 reviewers. Full-text reviews were then conducted of articles that passed the title and abstract screening phases. If applicable, conflicting decisions of inclusion or exclusion were to be resolved by a third author reviewing the article and making the final decision.

Data Abstraction

One reviewer conducted the data abstraction with a separate reviewer validating the abstraction. Data abstraction included title, first author, year of publication, study objective, study design, intervention, setting, reference period, statistical analyses, study outcomes, results, and key limitations. Quality assessment of the studies was conducted by 2 reviewers using the US Preventative Services Task Force Quality Assessment for randomized controlled trials and observational studies,[48] and The Economic Evaluation Bias Checklist for risk of bias in economic analyses.[49] The objective of this review was to evaluate existing data on the effect of blister packaging on medication adherence, health outcomes, health care resource utilization (HCRU), and health care costs in psychiatry. A meta-analysis was not feasible due to the included studies assessing medication adherence differently, not allowing for a quantitative assessment.

Results

The PubMed/Medline search returned 74 articles, whereas the Google Scholar Search yielded 2210 hits. After removing duplicates, 2251 articles and papers underwent review with 2145 removed due to nonrelevant titles (Figure). Of these, 106 abstracts were reviewed, and 31 underwent full-text reviews. In total, 5 articles met our inclusion criteria and were included in the review.[50-54] One article was identified in the PubMed/Medline search,[51] and 4 were identified in Google Scholar[50,52-54] with 3 of the Google Scholar articles not being indexed in PubMed.[50,52,53] No additional

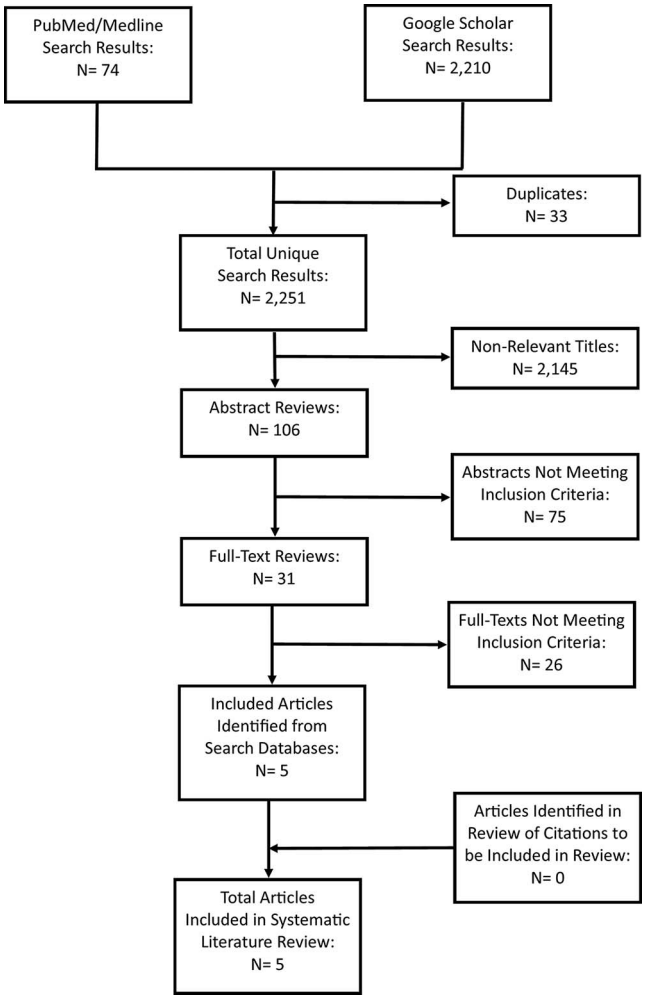

FIGURE: Flowchart of studies identified during the systematic literature review

articles were identified in the review of citations. Three of the articles centered around 1 pragmatic randomized controlled trial (pRCT) (Table 2).[50-52] Two of these articles described the study methodology and results: 1 being a peer-reviewed journal article and the other a published final government report providing additional methodological details and results.[50,51] The remaining article was a cost-utility analysis (CUA) using data from the pRCT assessing whether blister packaging medications for patients with psychiatric disorders is cost-effective.[52] The remaining 2 articles were studies that evaluated the effect of interventions to improve medication adherence in patients with psychiatric disorders with blister packaging or calendar packing medications as a part of the intervention.[53,54] The quality assessment rated the 3 clinical studies as fair quality, and the risk of bias assessment for the CUA found its risk of bias to be low. The following studies provide detailed insights into how blister packaging affects adherence and outcomes in psychiatric care alongside the pharmacoeconomic evaluation.

Clinical Study 1 and Government Report: Veteran Affairs Medication Adherence and Symptom Distress Assessment pRCT

A pRCT was conducted at a Veterans Affairs (VA) Medical Center in Colorado, including patients 18 to 89 years of age with a diagnosis of major affective disorder, posttraumatic stress disorder (PTSD), schizophrenia, or a combination of these disorders actively receiving at least 1 medication from the hospital pharmacy.[50,51] Patients were randomly assigned to receive either all of their prescribed medications in blister packages (n = 120) or all of their prescribed medications in pill bottles (n = 123) with a follow-up period of 12 months.[50,51] The mean age was 54 years in both treatment groups with 83% in the blister packaging group being male, whereas 91% were male in the control group.[50,51] The mean number of medications taken at enrollment was 8.4 (±SD 5.4).[51] The patient population consisted of 67% of patients with major affective disorder, 55% with PTSD, 38% with substance use, 37% with alcohol use, and 23% with bipolar disorder.[51] At 1-year follow-up, patients receiving blister packaged medications were 59% closer to perfect adherence (95% CI: 6.6% to 112.2%) compared with those that received the pill bottles with perfect adherence being defined in the study as 100% adherence during the assessed time frame.[50,51] When assessing adherence change from the 1-month to 12-month follow-up, patients with blister packages improved their adherence by 28.8%, whereas patients with pill bottles saw a decrease in adherence by 36.6% (difference in change: 65.4%, 95% CI: 5.7 to 126.1).[50,51] Assessing the effect of blister packaging on symptom distress (assessed by the Outcome Questionnaire), they found statistically significant improvements from month 1 to month 3 (difference in change 2.89, 95% CI: 0.412 to 5.52) and month 1 to month 6 (difference in change 5.77, 95% CI: 0.552 to 11.29), but these results were not deemed to be clinically significant. Nonsignificant improvements were seen from months 1 to 9 and months 1 to 12.[50,51]

Cost-Utility Analysis: Economic Evaluation of Blister Packaging in Psychiatry

Following the publication of the abovementioned pRCT, a CUA was conducted of this trial to assess the potential cost-effectiveness of blister packaging medications for patients with serious psychiatric disorders.[52] This CUA was conducted from the perspective of the Veterans Health Affairs (VHA), using a 12-month time horizon. The clinical inputs in the model were informed from the results of the abovementioned pRCT, whereas the costs were respective of costs incurred by the VHA. The main outcome was the incremental cost-effectiveness ratio (ICER) assessing the cost per quality adjusted life year (QALY).[52] QALYs were calculated from estimated utilities from participant-completed 36-item Short Form Health Survey.[52] The mean

TABLE 2: Included study demographic information

	Gutierrez[50,51]	Lavigne[52]	Samat[53]	Valenstein[54]
Study Design	Pragmatic randomized controlled trial	Cost utility analysis	Quasi-experimental pre-post study	Pragmatic randomized controlled trial
Patient population inclusion criteria	• Patients at a VHA hospital • Age 18 to 89 • Diagnosis of major affective disorder, PTSD, and/or schizophrenia	• Patient population and demographics are the same as those in the Gutierrez study in the previous column. • Perspective: VHA, time horizon: 12 months	• Patients at psychiatric hospital in Melaka • Age 18 to 60 • Stable schizophrenia who started oral antipsychotic drug ≥4 weeks prior to study	• Patients at a VHA hospital • Prescribed antipsychotic medications with ≥2 outpatient mental health visits in prior 12 months • Clinical diagnosis of schizophrenia, schizoaffective, or bipolar disorder • Long-term antipsychotic treatment • MPR <0.80 in prior 12 months
Intervention	Blister packaging all patient medications	Cost utility analysis using Gutierrez study to estimate ICER and QALYs	Blister packaging	Meds-Help: (1) blister packaging all patients medications, (2) a medication & packaging education session, (3) mailed refill reminders, (4) clinician notification when patients fail to refill within 7 to 10 days of fill date
Number of patients	243 total patients • 120 in the blister packaging group • 123 in pill bottle group	Not applicable (modeled on Gutierrez study population)	60 total patients • 27 blister packaging group • 33 control group	118 total patients • 58 to intervention including blister packaging • 60 control group
Patient demographics	Mean age: 54.4 years Male: 87% White Race: 47% African American Race: 36% Mean years in military: 4.9 years Mean number of medications at enrollment: 8.4 Major affective disorder: 67% Bipolar disorder: 23% PTSD: 55% Substance use 38% Alcohol abuse: 37%	Not applicable (modeling study)	Mean age: 39.4 years Male: 58.3% Malay Race: 50% Chinese Race: 46.7% 1 Medication: 56.7% 2 Medications: 28.3% ≥3 Medications: 15.0% Mean duration of illness: 12.7 years	Mean age: 49.9 years Men: 96.6% Nonwhite: 50.8% Schizophrenia: 66.9% Bipolar: 33.1% Substance use: 30.5%

BP = blister packaged; CAM = composite medication adherence; dic = difference in change; ICER = incremental cost-effectiveness ratio; MPR = medication possession ratio; OQ-45 = Outcome Questionnaire-45; QALY = quality adjusted life year; PTSD = posttraumatic stress disorder; SF-36 = 36-Item Short Form Survey; VHA = Veterans Health Affairs; WTP = willingness-to pay.

cumulative QALYs were numerically higher but not statistically different in the blister packaging group compared with the pill bottle group (0.591 versus 0.580; incremental difference: 0.011, 95% CI: −0.008 to 0.031).[52] Additionally, the mean cumulative costs were lower in the blister pack group than in the pill bottle group ($28 591 versus $30 732; difference: −$2140, 95% CI: −$9053 to $4773).[52] When calculating the ICER, blister packaging fell into quadrant 2 of the cost-effectiveness plane and was dominant (more effective, less costly); however, the results were not statistically significant as the probabilistic sensitivity analysis showed less than 75% of the simulations fell into quadrant 2.[52] According to the acceptability curves, blister packaging had a 77.5% chance of being cost-effective at a $50 000/QALY willingness-to-pay (WTP) threshold and an 87.8% chance of being cost-effective at a $300 000/QALY WTP threshold.[52] This was likely due to the marginal differences in both costs and effectiveness of blister packaging compared with the usual care arm. Whereas, in the base case, the results were dominant due to potential variation shown in the probabilistic sensitivity analysis, the results could enter quadrant 1 and exceed WTP in some scenarios.

Clinical Study 2: Blister Packaging Intervention Quasi-Experimental Study in Malaysia

A quasi-experimental study was conducted at the Psychiatric Clinic Hospital Melaka in Malaysia to assess the effect of a medications-unit-of-dose intervention on medication adherence in patients with schizophrenia.[53] Patients were included if they were 18 to 60 years old, had stable schizophrenia (according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition), and started their oral antipsychotic medication regimen at least 4 weeks before the study commenced.[53] Patients were alternately placed into 2 groups in order of recruitment: the intervention group, which received medications packaged in a unit-of-dose booklet (blister package) that included a patient medication summary and refill reminder (n = 27), and the control group in which patients received usual care defined as standard communication and counseling (n = 33).[53] No information was provided as to the medication dispensing method of the control group, other than it was "usual care."[53] There were some demographical differences between the 2 treatment groups with a mean age of 36.9 years for the intervention group and 41.5 years for the control, 41% male in the intervention group and 73% in the control group, and 82% were single in the intervention group and 61% in the control group.[53] However, there were minimal differences in baseline clinical information with the duration of illness being 13.0 years (SD: 9.1) versus 12.5 years (SD: 10.6) and 55.6% versus 57.6% of patients on 1 medication between the intervention and the control groups, resepectively.[53] After adjusting for baseline characteristics, the intervention group had a significantly higher pill count percentage at baseline than the control group (93.2%, 95% CI: 89.8to 94.3 versus 87.9%, 95% CI: 84.9 to 90.9), which continued to be present throughout month 3 (97.5%, 95% CI: 93.5 to 101.5 versus 89.5%, 95% CI: 85.9 to 93.1) and month 5 (100.2%, 95% CI: 97.9 to 102.5 versus 92.3%, 95% CI: 90.2 to 94.4).[53] Pill count percentage was calculated as the (number of dosage units dispensed minus the number of dosage units remaining) divided by (the prescribed number of dosage units per day multiplied by the number of days between visits), all multiplied by 100%.[53] Compared with baseline, the intervention group saw significant improvements in pill count percentages from baseline (defined as adjusted mean difference) at 3 months (−4.3, 95% CI: −8.2 to −0.4) and at 5 months (−7.6, 95% CI: −11.2 to −4.0), whereas there was no significant improvement in the control group at 3 months (−1.5, 95% CI: −7.7 to 4.6) or 5 months (−3.8, −8.2 to 0.7).[53] The intervention group also saw significant improvements (defined as adjusted mean difference) in the Medication Adherence Rating Scale score from baseline at 3 months (−0.7, 95% CI: −1.3 to −0.1) and at 5 months (−0.7, −1.4 to −0.0), whereas there was no significant difference in the control group seen at 3 months (−0.1, 95% CI: −0.6 to 0.4) or at 5 months (0.2, 95% CI: −0.3 to 0.7).[53]

Clinical Study 3: Veteran Affairs Pharmacy-Based Intervention RCT

An RCT was conducted among VA patients with serious psychiatric disorders to assess the effect of a pharmacy-based intervention titled Meds-Help on antipsychotic medication adherence and other clinical outcomes.[54] Patients were included if they had at least 2 outpatient mental health visits in the past 12 months; had a clinical diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder; had a long-term antipsychotic treatment plan; and were nonadherent to antipsychotic medications (adherence defined as medication possession ratio (MPR) <80% in the prior 12 months) with 118 patients included in the study.[54] Patients were randomized to the usual care group or Meds-Help.[54] The Meds-Help intervention consisted of 4 parts: unit-of-use blister packaging all of the patient's medications (for psychiatric disorders as well as general disorders), an education session for medication and packaging, refill reminders that were mailed out to patients 2 weeks prior to their scheduled refill date, and notification to the patient's prescribing clinician when the patient did not refill the antipsychotic medication 7 to 10 days past the expected fill date.[54] No information was provided to describe how medications were dispensed and packaged for patients in the usual care group.[54] The patient population consisted of 96.6% men and a mean age of 50 years old, and 66.9% of patients had schizophrenia, 33.1% had bipolar disorder, and 30.5% had substance use.[54] Whereas MPR was similar at baseline between the intervention and control groups (MPR: 54% versus 55%, $P = .7676$), the intervention group had significantly higher adherence at 6 months (MPR: 91%

versus 64%, $P < .0001$) and at 12 months (MPR: 86% versus 62%, $P < .001$).[54] A composite adherence measure (CAM) was also assessed. Patients were deemed adherent with the CAM if (1) MPR $\geq$ 0.8, (2) patients reported they either "always" took their antipsychotic medications or only missed their dose "a couple of times," and (3) their blood test indicated the presence of some antipsychotic medication. For CAM, the intervention group saw significantly higher adherence at 6 months (50.0% versus 17.0%, $P = .0003$) and nonsignificantly higher adherence at 12 months (34.0% versus 17.7%, $P = .06$).[54] In multivariable linear regression analyses, the only variables associated with statistically significant improvements in MPR (seen at both 6 and 12 months) were baseline MPR (β at 6 months: 0.67, $P < .0001$; β at 12 months: 0.53, $P = .0009$) and the intervention received (Meds-Help versus usual care) (β at 6 months: 0.28, $P < .0001$; β at 12 months: 0.26, $P < .0001$).[54] There were no significant differences between the 2 groups on the Positive and Negative Symptoms Scale, Quality of Well-Being Scale, or Client Satisfaction Questionnaire.[54]

Discussion

This review identified 3 clinical studies and 1 CUA assessing the effect of blister packaging medications in psychiatric settings.[50-54] All 3 of the clinical studies showed that blister packaging significantly increased rates of medication adherence compared with standard medication filling,[50,51,53,54] whereas the economic analysis found blister packaging medications to be cost-saving in the base case although the results were not statistically significant.[52] Minimal results were identified related to the effect that blister packaging has on clinical outcomes and/or quality of life. The identified studies collectively show that blister packaging medications in psychiatry is an intervention that is effective at helping to promote and improve medication adherence; however, more data is needed to assess its effect on clinical outcomes for patients.

The significance of medication adherence in psychiatry cannot be overstated as treatment success is closely linked to adherence. For instance, an analysis of commercial claims data from 2000 to 2006 of patients hospitalized with bipolar disorder and prescribed an antipsychotic within 14 days of discharge found that patients with an MPR of at least 75% had a significantly lower risk of all-cause rehospitalization (odds ratio [OR]: 0.730, 95% CI: 0.580 to 0.919) and a significantly lower risk of a mental health–related rehospitalization (OR: 0.759, 95% CI: 0.603 to 0.955).[4] An analysis of Truven Health Analytics MarketScan Medicare databases from January 2005 to September 2010 of patients 65 years or older with schizophrenia found that patients with high adherence (MPR $\geq$ 70%) had significantly lower rates of all-cause hospitalizations (0.68 versus 0.44, $P = .015$) and relapse-specific hospitalizations (0.22 versus 0.11, $P = .028$).[17] A claims analysis of the Truven Health Marketscan Research database was conducted of commercially insured patients initiating buprenorphine/naloxone for the treatment of opioid use disorder (OUD) revealed that patients who were adherent to treatment (proportion of days covered of at least 80%) had significantly lower adjusted odds of all-cause and OUD-specific health care events (adjusted OR [aOR]: 0.62, 95% CI: 0.52 to 0.74; aOR: 0.44, 95% CI: 0.31 to 0.63, respectively) as well as significantly lower mean per-patient per-month inpatient costs ($334.59 versus $759.10, $P < .001$) and outpatient costs ($627.11 versus $1189.85, $P < .001$).[55]

Medication adherence in patients with psychiatric disorders has historically been lower than other chronic disorders with adherence rates reported in the literature ranging from 12% to 88%.[2-9] Whereas blister packaging cannot address all potential reasons for medication nonadherence, it may be able to aid in ensuring proper medication intake and mitigating forgetfulness. Although it may not benefit every patient, its potential to assist some patients merits further consideration. As the studies included in this review show, blister packaging significantly improved various dimensions of medication adherence,[50,51,53,54] supporting its potential utility in this population.

Blister packaging has historically been an effective option for promoting medication adherence across a variety of chronic disorders.[56] Effectiveness is also seen across a composite group of patients with various chronic disorders. In a retrospective pre/post study of patients in Alaska, MPR increased from 67.4% (SD: 18.2) to 86.0% (SD: 17.1) ($P = .000117$) after implementing blister packaging of patients' medications.[57] This patient population included 10.3% of patients prescribed psychologic/neurologic medications along with 16.0% prescribed antihypertensives, 13.1% prescribed antidiabetics, and 6.4% prescribed medications for hyperlipidemia among others.[57] Whereas this literature review did not find any studies that measured the effect of blister packaging on clinical outcomes, all of the studies identified did show improvements in adherence rates.[50,51,53,54] Although medication adherence is only a surrogate outcome to specified clinical outcomes, there are validated quality measures, including Healthcare Effectiveness Data and Information Set measures that assess medication adherence rates for antidepressants and antipsychotics,[58-60] along with several research studies linking treatment adherence to clinical success.[4,16-22]

Whereas the studies identified in this review only assessed increases in medication adherence from blister packaging medications, they included only certain psychiatric disorders. Across the 3 clinical studies, the disease states specified in the studies' inclusion criteria included PTSD, schizophrenia, major affective disorder, schizoaffective

disorder, or bipolar disorder.[50,51,53,54] Although there is some variety of the assessed psychiatric disorders, it does not cover the entire breadth of psychiatry. Disorders not assessed include depression, anxiety disorders, substance use disorders, and borderline personality disorder among many others. Due to the clinical differences of the varying disease states in psychiatry, it is uncertain what the potential effect of blister packaging would have on medication adherence without being directly assessed. However, the fact that the 3 clinical studies identified in this space included several different clinical disorders helps to add promise to its use across psychiatry. Additionally, the included studies assessed a small number of patients ranging from 27 to 120 patients in the blister packaging intervention group or 60 to 243 total patients assessed in the study.[50,51,53,54] Whereas the number of patients in the study was sufficient to detect statistical differences, larger sized studies are needed.

Although none of the clinical studies assessed economic outcomes, 1 included study was a CUA attempting to measure the cost-effectiveness of blister packaging psychiatric medications using clinical data from the VA pRCT study.[52] Using a 1-year time horizon from the VHA perspective, they found that blister packaging fell into quadrant 2 of the cost-effectiveness plane and was dominant (more effective, less costly) with the results approaching but failing to be statistically significant. Costs included in the analysis were costs of blister packaging materials and labor time to fill the materials as well as drug and medical costs. A difficulty in interpreting CUA for nonpharmacologic agents is that, when the agent of interest falls in either quadrant 1 (more costly, more effective) or quadrant 3 (less costly, less effective) of the cost-effectiveness plane, it is difficult to determine what is considered cost-effective as there are no clearly established WTP thresholds. Whereas well-established WTP in the United States for medications are anywhere from $50 000/QALY to $150 000/QALY,[61-64] there is no threshold for nonpharmacologic interventions with the results difficult to interpret for respective stakeholders. Although this CUA base-case result was cost saving and fell in quadrant 2, the results were not statistically significant. Overall, there were small differences in mean QALYs with 0.59 for the blister package group compared with 0.58 for the usual group along with small differences in cost ($28 591 versus $30 732).[49] Even though this CUA is limited in its findings, it provides some data showing the economic effect of blister packaging with more research needed in this area. No CUA/cost-effectiveness analyses were identified in the literature that assessed the potential cost-effectiveness of blister packaging in other chronic disease states. As a result, it is difficult to compare how cost-effective blister packaging is in the psychiatric space compared with other disorders.

Whereas the evidence demonstrating the effectiveness of blister packaging found in this space is promising, further studies and research are needed to add more certainty and generalizability to these findings. Studies such as RCTs, pRCTs, and pre-post observational trials conducted in large institutions and/or clinical practices assessing a variety of patients with a large sample size would be recommended. Additionally, further research should investigate the effect of blister packaging in psychiatric disorders not yet studied, including but not limited to anxiety disorders and substance use disorder. Research should also encompass various stages of disease progression and include demographically diverse populations to allow for stratification and subgroup analyses. These analyses may help identify treatment groups that could benefit from this intervention more so than others. Studies should aim to assess not only the effect on medication adherence definitions, but also the effect on treatment success, disease status, specific clinical endpoints, HCRU, and health care costs. In addition to more clinical studies, there is a need for more economic analyses demonstrating the financial effect of blister packaging in psychiatry. These financial analyses could significantly influence the adoption and use of this intervention, specifically if it is shown to have a positive return on investment and/or is found to be cost-effective.

There are several limitations with this review in addition to those already discussed. First, the review was both targeted and systematic, which allows for the possibility of inadvertently omitting studies that met the inclusion criteria but were not indexed in the assessed databases. Nevertheless, the review of 2 different databases and the citation review of all full texts should help to minimize this risk. Another limitation, as previously mentioned, is that only 3 clinical studies were included in this review, and they were small in scale, limiting the potential generalizability of the results. Medication adherence is effectively a surrogate outcome, and although literature shows correlations between medication adherence and improved health outcomes and reduced health care costs, it remains uncertain whether blister packaging these medications will ultimately affect health outcomes and treatment success in this specific setting.

Three clinical studies were identified that assessed the effect of blister packaging medications in psychiatry, all demonstrating that blister packaging improved medication adherence. Additionally, 1 economic analysis showed that blister packaging psychiatric medications was both less costly and more effective. The evidence presented in this review supports the positive effect for blister packaging in a psychiatric population. Although the studies were limited in number and scale, further research with larger study sizes is needed to comprehensively assess the effect of blister packaging

medications in psychiatry, including their effects on clinical outcomes and health care costs.

References

1. Malik M, Kumari S, Manalai P. Treatment nonadherence: an epidemic hidden in plain sight. Psychiatric Times. 2020;37(3):25-6. Available from: https://www.psychiatrictimes.com/view/treatment-nonadherence-epidemic-hidden-plain-sight
2. Ghosh P, Balasundaram S, Sankaran A, Chandrasekaran V, Sarkar S, Choudhury S. Factors associated with medication nonadherence among patients with severe mental disorder—a cross sectional study in a tertiary care centre. Explor Res Clin Soc Pharm. 2022;7:100178. DOI: 10.1016/j.rcsop.2022.100178
3. Mert DG, Turgut NH, Kelleci M, Semiz M. Perspectives on reasons of medication nonadherence in psychiatric patients. Patient Prefer Adherence. 2015;9:87-93. DOI: 10.2147/PPA.S75013
4. Hassan M, Lage MJ. Risk of rehospitalization among bipolar disorder patients who are nonadherent to antipsychotic therapy after hospital discharge. Am J Health Syst Pharm. 2009;66(4):358-65. DOI: 10.2146/ajhp080374
5. Lintunen J, Lähteenvuo M, Tanskanen A, Tiihonen J, Taipale H. Non-adherence to mood stabilizers and antipsychotics among persons with bipolar disorder—a nationwide cohort study. J Affect Disord. 2023;333:403-8. DOI: 10.1016/j.jad.2023.04.030
6. Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Lindamer L, Garcia P, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry. 2004;161(4):692-9. DOI: 10.1176/appi.ajp.161.4.692
7. Lucca JM, Ramesh M, Parthasarathi G, Ram D. Incidence and factors associated with medication nonadherence in patients with mental illness: a cross-sectional study. J Postgrad Med. 2015;61(4):251-6. DOI: 10.4103/0022-3859.166514
8. Semahegn A, Torpey K, Manu A, Assefa N, Tesfaye G, Ankomah A. Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis. Syst Rev. 2020;9(1):17. DOI: 10.1186/s13643-020-1274-3
9. Zeleke TK, Birhane W, Gubae K, Kebede B, Abebe RB. Navigating the challenges: predictors of non-adherence to psychotropic medications among patients with severe mental illnesses in Ethiopia. Patient Prefer Adherence. 2023;17:2877-90. DOI: 10.2147/PPA.S422659
10. Malee K, Williams P, Montepiedra G, McCabe M, Nichols S, Sirois PA, et al. Medication adherence in children and adolescents with HIV infection: associations with behavioral impairment. AIDS Patient Care STDS. 2011;25(3):191-200. DOI: 10.1089/apc.2010.0181
11. Leslie RS, Erickson SC, Patel BV. Patient characteristics and medication burden affect adherence among seniors. Am J Pharm Benefits. 2014;6(4):183-8.
12. Marcum ZA, Gellad WF. Medication adherence to multidrug regimens. Clin Geriatr Med. 2012;28(2):287-300. DOI: 10.1016/j.cger.2012.01.008
13. Hughes CM. Medication non-adherence in the elderly: how big is the problem? Drugs Aging. 2004;21(12):793-811. DOI: 10.2165/00002512-200421120-00004
14. Telinoiu CM. Measures adherence with antidepressant medication: comparison of HEDIS and PDC methodologies [master's thesis]. Kingston, (RI): University of Rhode Island, 2016. Available from: https://digitalcommons.uri.edu/cgi/viewcontent.cgi?article=1844&context=theses
15. Chapman SC, Horne R. Medication nonadherence and psychiatry. Curr Opin Psychiatry. 2013;26(5):446-52. DOI: 10.1097/YCO.0b013e3283642da4
16. Hong J, Reed C, Novick D, Haro JM, Aguado J. Clinical and economic consequences of medication nonadherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. Psychiatry Res 2011;190:110-4. DOI: 10.1016/j.psychres.2011.04.016
17. Offord S, Lin J, Wong B, Mirski D, Baker RA. Impact of oral antipsychotic medication adherence on healthcare resource utilization among schizophrenia patients with Medicare coverage. Community Ment Health J. 2013;49(6):625-9. DOI: 10.1007/s10597-013-9638-y
18. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin. 2009;25(9):2303-10. DOI: 10.1185/03007990903126833
19. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. Schizophr. Bull. 1997;23:637-51. DOI: 10.1093/schbul/23.4.637
20. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018;8(1):e016982. DOI: 10.1136/bmjopen-2017-016982
21. Jiang Y, Ni W. Estimating the impact of adherence to and persistence with atypical antipsychotic therapy on health care costs and risk of hospitalization. Pharmacotherapy. 2015;35(9):813-22. DOI: 10.1002/phar.1634
22. Becker MA, Young MS, Ochshorn E, Diamond RJ. The relationship of antipsychotic medication class and adherence with treatment outcomes and costs for Florida Medicaid beneficiaries with schizophrenia. Adm Policy Ment Health. 2007;34(3):307-14. DOI: 10.1007/s10488-006-0108-5
23. Zedler BK, Kakad P, Colilla S, Murrelle L, Shah NR. Does packaging with a calendar feature improve adherence to self-administered medication for long-term use? A systematic review. Clin Ther. 2011;33(1):62-73. DOI: 10.1016/j.clinthera.2011.02.003
24. Ágh T, Hiligsmann M, Borah B, Beaudart C, Turcu-Stiolica A, Manias E, et al. Systematic review of outcomes for assessment of medication adherence enhancing interventions: an ISPOR Special Interest Group Report. Value Health. 2024;27(2):133-42. DOI: 10.1016/j.jval.2023.10.016
25. Conn VS, Ruppar TM, Chan KC, Dunbar-Jacob J, Pepper GA, De Geest S. Packaging interventions to increase medication adherence: systematic review and meta-analysis. Curr Med Res Opin. 2015;31(1):145-60. DOI: 10.1185/03007995.2014.978939
26. Zedler BK, Joyce A, Murrelle L, Kakad P, Harpe SE. A pharmacoepidemiologic analysis of the impact of calendar packaging on adherence to self-administered medications for long-term use. Clin Ther. 2011;33(5):581-97. DOI: 10.1016/j.clinthera.2011.04.020
27. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA. 2006;296(21):2563-71. DOI: 10.1001/jama.296.21.joc60162
28. Leslie RS, Gilmer T, Natarajan L, Hovell M. A multichannel medication adherence intervention influences patient and prescriber behavior. J Manag Care Spec Pharm. 2016;22(5):526e538. DOI: 10.18553/jmcp.2016.22.5.526
29. Leslie RS, Tirado B, Patel BV, Rein PJ. Evaluation of an integrated adherence program aimed to increase Medicare part D star rating measures. J Manag Care Spec Pharm. 2014;20(12):1193e1203. DOI: 10.18553/jmcp.2014.20.12.1193
30. Pinto S, Simon A, Osundina F, Jordan M, Ching D. Study to measure the impact of pharmacists and pharmacy services (STOMPP) on medication non-adherence: medication adherence and clinical

outcomes. INNOVATIONS Pharmacy. 2018;9(1):1-11. DOI: 10.24926/iip.v9i1.1104
31. Daly CJ, Verrall K, Jacobs DM. Impact of community pharmacist interventions with managed care to improve medication adherence. J Pharm Pract. 2021;34(5):694e702. DOI: 10.1177/0897190019896505
32. Hong M, Esse T, Vadhariya A, Gallardo E, Fosshat MA, Mamvou J, et al. Evaluating success factors of a medication adherence tracker pilot program in improving part D medication adherence metrics in a Medicare advantage plan: importance of provider engagement. J Manag Care Spec Pharm. 2020;26(5):662e667. DOI: 10.18553/jmcp.2020.26.5.662
33. Smith JY, Leslie RS, Patel BV, Kucharski C, Joseph SB, Sow M. E-prescribing with decision support is associated with improvements in medication adherence. Am J Pharm. 2016;8(4):133-40.
34. Hale G, Moreau C, Joseph T, Phyu J, Merly N, Tadros N, et al. Improving medication adherence in an ACO primary care office with a pharmacist-led clinic: a report from the ACORN SEED. J Pharm Pract. 2021;34:888e893. DOI: 10.1177/0897190020934271
35. Neiman AB, Ruppar T, Ho M, Garber L, Weidle PJ, Hong Y, et al. CDC grand rounds: improving medication adherence for chronic disease management—innovations and opportunities. Morb Mortal Wkly Rep. 2017;66(45):1248-51. DOI: 10.15585/mmwr.mm6645a2
36. Schneider PJ, Murphy JE, Pedersen CA. Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients. J Am Pharm Assoc (2003). 2008;48(1):58-63. DOI: 10.1331/JAPhA.2008.07040
37. Tan BY, Shafie AA, Hassali MAA, Saleem F. Assessment of medication adherence and the costs associated with a calendar blister pack intervention among hypertensive patients in Malaysia: a randomized controlled trial. SAGE Open Med. 2017;5:2050312117709189. DOI: 10.1177/2050312117709189
38. Simmons D, Upjohn M, Gamble GD. Can medication packaging improve glycemic control and blood pressure in type 2 diabetes? Results from a randomized controlled trial. Diabetes Care. 2000;23(2):153-6. DOI: 10.2337/diacare.23.2.153
39. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. Ann Intern Med 1997;126:376-80. DOI: 10.7326/0003-4819-126-5-199703010-00006
40. Mandrik OL, Severens JLH, Bardach A, Ghabri S, Hamel C, Mathes T, et al. Critical appraisal of systematic reviews with costs and cost-effectiveness outcomes: an ISPOR Good Practices Task Force Report. Value Health. 2021;24(4):463-72. DOI: 10.1016/j.jval.2021.01.002
41. Pati D, Lorusso LN. How to write a systematic review of the literature. HERD 2018;11:15-30. DOI: 10.1177/1937586717747384
42. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372(71). DOI: 10.1136/bmj.n71
43. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. DOI: 10.1136/bmj.b2535
44. Centre for Reviews and Dissemination: Systematic reviews: CRD's guidance for undertaking systematic reviews in health care. York: University of York. Centre for Reviews and Dissemination, 2009. Available from: http://www.york.ac.uk/inst/crd/index_guidance.htm
45. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. London: The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org
46. Greenland S, O'Rourke K. Meta-analysis. In: Rothman KJ, Greenland S, Lash TL, editors. Modern epidemiology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 652-82.
47. Cooper C, Booth A, Varley-Campbell J, Britten N, Garside R. Defining the process to literature searching in systematic reviews: a literature review of guidance and supporting studies. BMC Med Res Methodol. 2018;18(1):85. DOI: 10.1186/s12874-018-0545-3
48. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. Agency for Healthcare Research and Quality, 2008, Available from: https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual
49. Adarkwah CC, van Gils PF, Hiligsmann M, Evers SM. Risk of bias in model-based economic evaluations: the ECOBIAS checklist. Expert Rev Pharmacoecon Outcomes Res. 2016;16(4):513-23. DOI: 10.1586/14737167.2015.1103185
50. Gutierrez PM, Brenner LA, Wortzel H, Leitner R, Harwood JE. Blister packaging medication to increase treatment adherence and clinical response: impact on suicide-related morbidity and mortality. U.S. Army Medical Research and Materiel Command [2014 Dec; cited 2024 May 18]. Available from: https://apps.dtic.mil/sti/citations/ADA618415
51. Gutierrez PM, Wortzel HS, Forster JE, Leitner RA, Hostetter TA, Brenner LA. Blister packaging medication increases treatment adherence in psychiatric patients. J Psychiatr Pract. 2017;23(5):320-7. DOI: 10.1097/PRA.0000000000000252
52. Lavigne JE, Falbo K, Gutierrez PM. Cost–utility analysis of blister packaging all outpatient medications for veterans with bipolar disorder, major affective disorder, post-traumatic stress disorder or schizophrenia. J Pharmaceutical Health Services Res. 2019;10(4):401-6. DOI: 10.1111/jphs.12324
53. Samat SF, Choong KS, Sa'ad US, Baharudin N. Impact of pharmacist intervention using MEDS-UOD on medication adherence among schizophrenia patients. Pharmacy Res Rep. 2023; 6(2):1-8.
54. Valenstein M, Kavanagh J, Lee T, Reilly P, Dalack GW, Grabowski J, et al. Using a pharmacy-based intervention to improve antipsychotic adherence among patients with serious mental illness. Schizophr Bull. 2011;37(4):727-36. DOI: 10.1093/schbul/sbp121
55. Liao S, Jang S, Tharp JA, Lester NA. Relationship between medication adherence for opioid use disorder and health care costs and health care events in a claims dataset. J Subst Use Addict Treat. 2023;154:209139. DOI: 10.1016/j.josat.2023.209139
56. Heneghan CJ, Glasziou P, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database Syst Rev. 2006;(1):CD005025. DOI: 10.1002/14651858.CD005025.pub2 Update in: Cochrane Database Syst Rev. 2011;(9):CD005025. DOI: 10.1002/14651858.CD005025.pub3
57. Navin LS. Blister packaging medications for adherence for American Indians/Alaska Natives in the outpatient setting. J Pharm Pract. 2021;34(1):97-102. DOI: 10.1177/0897190019851357
58. National Committee for Quality Assurance. HEDIS Measures and Technical Resources. National Committee for Quality Assurance, 2024. Available from: https://www.ncqa.org/hedis/measures/.
59. Medicaid. Core set of adult health care quality measures. Centers for Medicare & Medicaid Services, 2024. Available from: https://www.medicaid.gov/medicaid/quality-of-care/performance-measurement/adult-and-child-health-care-quality-measures/adult-health-care-quality-measures/index.html
60. National Quality Forum. Endorsement Summary: Behavioral Health Measures. National Quality Forum, 2012 November. Available from: https://www.qualityforum.org/news_and_resources/endorsement_summaries/endorsement_summaries.aspx
61. Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association

Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129(22):2329-45. DOI: 10.1161/CIR.0000000000000042
62. CVS Health. Current and new approaches to making drugs more affordable, August 2018. Available from: https://cvshealth.com/sites/default/files/cvs-health-current-and-new-approaches-to-making-drugs-more-affordable.pdf
63. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. Institute for Clinical and Economic Review, 2022 February. Available from: https://icer.org/wp-content/uploads/2020/11/ICER_2020_2023_VAF_02032022.pdf
64. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371(9):796-7. DOI: 10.1056/NEJMp1405158