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REVIEW ARTICLE

Evaluating the Impact of Pharmacists on Clinical Outcomes and Adherence in Patients with Mental Illness: A Literature Review

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ABSTRACT

Purpose: The purpose of this literature review is to investigate the role of pharmacists in improving clinical outcomes and adherence to psychotropic medications in patients with mental illness. The majority of patients tend to stop taking their medications due to the delayed effects or adverse events. It has been established that pharmacists have a positive effect on patients' clinical outcomes in different chronic disease states other than mental illness. There is also a stigma associated with how comfortable pharmacists are on counseling patients about psychotropic medications. This literature review will evaluate the level of pharmacists' involvement in treating patients with mental illness as well as strategies used to achieve persistence and compliance with therapy.

Methods: A PubMed search was conducted to identify articles related to mental illness and pharmacists. MeSH terms included "antidepressants", "adherence", "pharmacists", and "bipolar disorder". A free-text search was conducted using the same terms and to search for the most updated American Psychiatric Association practice guidelines. The National Institute of Mental Health database was searched for current mental health statistics in the United States. Collectively, 62 results returned for the MeSh search. This review included studies on adults with mental disorders who were evaluated by pharmacists for adherence and clinical outcomes between the years of 1995-2019. The results of five clinical trials assessing the role of pharmacists in adherence to psychotropic medications will be discussed in this literature review.

Results: The clinical trials included in this review showed a statistically significant increase in adherence to psychotropic medications associated with pharmacists' interventions. The results were not statistically significant for the clinical outcomes in most studies but presented positive improvements in the inpatient and outpatient settings. Canales *et al*. results showed that patients receiving pharmacists' interventions in the inpatient setting had >30% improved clinical outcomes measured by different rating scales. The results of Valenstein *et al*. study conducted at Veteran Affairs clinics were statistically significant for adherence improvement presented by a 25% increase in medication possession ratio. Aljumah *et al*. clinical trial had a 18% increase in adherence associated with pharmacist interventions. The EMDADER-TAB trial resulted in a statistically significant decrease in ER visits, significant improvement of the depression symptoms, and overall improvement of severity of symptoms.

Conclusion: Mental illness should be treated as any other medical condition that requires interventions whenever clinical outcomes are not optimal. Pharmacists have the skills to evaluate clinical symptoms of different psychiatric disorders as well as the knowledge on therapeutic treatments necessary for the optimization of medication use.

Keywords: Adherence in Patients, Pharmacists, Mental illness.

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INTRODUCTION

Data presented by the National Institute of Mental Health (NIMH) shows that 18.9% of adults in the United States have some type of mental illness, and there were twice as many suicides as homicides in 2017.[1] Approximately 15% of patients with the inadequately treated major depressive disorder die by suicide. Mental illness is also the leading cause of disability in the United States in patients between 15 to 44 of age.[1] This calls for more efforts to improve treatment outcomes within different healthcare settings and to exclude the stigma surrounding psychiatric disorders. Erku *et al*. conducted a study in 2016 to evaluate the role of pharmacists' medication therapy management on the rates of adherence to diabetic medications.[2] The study resulted in a statically significant improvement of adherence and a reduction in hospital admissions. Goruntla *et al*. randomized control trial evaluated the role of pharmacists' direct counseling on the clinical outcomes for patients with type II diabetes.[3] Pharmacists' follow up, and direct counseling had a statistically significant effect on cholesterol, blood pressure, and glycemic control. Still, the role of pharmacists in mental illness is not as clearly defined as in other disease states, which led to the conduction of this literature review. A recent qualitative study involving community pharmacists was conducted in Canada, to evaluate the perception of their practice regarding patients on antidepressants.[4] Pharmacists were

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questioned on their practice with new antidepressant prescriptions, pharmacy practice for refills, and their insight on the revolution of the role of pharmacists. The result showed that the most common challenges community pharmacists are faced are "time and money constraints, already compensating for shortcomings in the healthcare system, and barriers to follow up with patients for the full length of treatment".[4] Community pharmacists in this study recommended clear guidelines to monitor patients and improve patient education tools. Pharmacists are the drug-knowledge backbone of the healthcare team, and their recommendations influence the decisions of healthcare teams. Pharmacists can help patients maintain a desirable mental health status, which would reflect on their overall physical health and quality of life. Pharmacists' accessibility builds trust and can open the door for more interventions that lead to better remission rates. The efficacy of different pharmacological options has been proven for different psychiatric indications. However, the misuse of drugs has been an issue that leads to the failure of effective treatment options. Adherence to psychiatric medications is very important to control the symptoms and to improve patients' quality of life. The American Psychiatric Association (APA) recommends treating patients with major depressive disorder for at least 6-12 months.[5] Results of a retrospective analysis evaluating the persistence and adherence to antidepressants in insured patients in the United States showed that only 21% of patients continue their medication therapy for 12 months.[6] This was hypothesized to the perceived or experienced clinical benefits to patients, and called for further investigation of the role of providers.

Moreover, about 40% of patients of the Veterans Affairs Department with schizophrenia are wholly or partially nonadherent to therapy, and approximately half of the patients with bipolar disorders do not get enough supplies for the proper administration of their mood stabilizers.[7,8] Pharmacists are the most accessible healthcare providers to patients; therefore, they can efficiently participate in the management of their chronic diseases when processes are put in place. The objective of this study is to investigate the role of pharmacists in improving clinical outcomes and adherence to psychotropic medications in patients with mental illness.

METHODS

A PubMed search was conducted to identify articles related to mental illness and pharmacists. MeSH terms included "antidepressants", "adherence", "pharmacists", and "bipolar disorder". A free-text search was conducted using the same terms and to search for the most updated APA practice guidelines. The NIMH database was searched for current mental health statistics in the United States. Collectively, 62 results returned for the MeSh search. This review included studies on adults with mental disorders who were evaluated by pharmacists for adherence and clinical outcomes between the years of 1995-2019. The results of five clinical trials assessing the role of pharmacists in adherence to psychotropic medications will be discussed in this literature review.

RESULTS

Canales *et al*. published an intervention-control clinical trial to evaluate the role of pharmacists on the improvement of patients with psychiatric conditions in the inpatient acute care setting.[9] The study was conducted at a 350-bed hospital in Texas with phase I being the control group (October 1996-March 1997) and Phase II being the intervention group (May-December 1997). They enrolled 92 patients in the study, including patients with schizophrenia, bipolar disorder, major depressive disorder, and schizoaffective disorder. Psychotropic treatments received were similar between groups with selective serotonin reuptake inhibitors, risperidone, divalproex, and lithium being most commonly prescribed. Risperidone was more prescribed in the intervention group. There were more females than males enrolled in both groups with no difference in age being 35.9 ± 9.24 in the control group and 35.1 ± 9.76 in the intervention group. There were 36 Caucasians in control group and 27 intervention group. African-Americans were 5 control group and 11 in the intervention group. Hispanics were 7 in the control group and five intervention group. The intervention group received intensive pharmaceutical services, including pharmacists attending team meetings, performing clinical assessments, reviewing medication-administration records, providing recommendations, monitoring for adverse effects, and counseling patients before discharge. The control group, on the other hand, received "traditional centralized pharmaceutical services with physician requested pharmacotherapy".[9] Outcomes were measured by evaluating clinical response using objective rating scales, length of stay, adverse events, and patient compliance with primary care physician follow up visits. Clinical outcome assessments were performed within 72 hours of admission and before discharge in both study groups. The rating scales used were the brief psychiatric rating scale (BPRS) that measures psychiatric symptoms including anxiety and depression, the clinical global impressions scale (CGI) that measures symptoms' severity and response to treatment, the hamilton psychiatric rating scale for depression (HAM-D) that

measures the level of depression, the mini-mental state exam (MMSE) for cognitive function, the abnormal involuntary movement scale (AIMS), the barnes rating scale for drug-induced akathisia, and the simpson-angus rating scale for drug-induced extrapyramidal symptoms. The Lehman quality Life Interview was used to measure differences in quality of life. The modified systematic assessment for treatment emergent events (SAFTEE) was administered to record the rate of adverse events. Patients' attending their first outpatient follow up appointment after discharge was used as a measure of compliance. The results of the intervention group showed that 93% of patients had ≥20% improvement of BPRS scores ($p = 0.024$), 62% had ≥30% improvement of BPRS scores ($p = 0.002$), and 22% had ≥40 improvements of their BPRS scores ($p < 0.001$). Improvement of the HAM-D score was 65% in the intervention group and 9% in the control group ($p = 0.003$). Statistically significant lower side effects profile was documented in the intervention group based on the AIMS, the Barnes Rating Scale for Drug-Induced Akathisia, and the Simpson-Angus Rating Scale for Drug-Induced Extrapyramidal Symptoms Scale. The authors stated that "improvements in scores on these scales imply not only improved safety for patients but also future increased medication compliance and decreased hospitalization cost. This is clinically relevant since the occurrence of adverse events is strongly associated with medication noncompliance, subsequent relapse and rehospitalization, and higher cost of hospitalization".[9] A limitation of this study is that it conducted in a randomized parallel fashion due to the availability of only five psychiatrists in the hospital working alongside with the pharmacists. Another limitation would be the influence on the objectivity of the rating scales because they were performed by the pharmacist providing the clinical services.

Finley *et al*. published an intervention-control study conducted at Kaiser Permanente Primary Care Clinic in California in 1998, evaluating the role of pharmacists in improving outcomes of patients with depression within a collaborative practice.[10] The control group included 129 patients on antidepressants treated by their primary care providers (PCPs) only. The intervention group included 91 patients who were referred to pharmacists by their PCPs for an assessment of their mental health history, symptoms, and stressors, using the Inventory for Depressive Symptoms (IDS) scale, at 3 and 6 months. Patients received medication therapy management services by the pharmacists through a combination of scheduled face to face visits and telephone follow-up calls. Pharmacists conducted interviews that would last around 20–30 minutes on the same day an antidepressant was prescribed. These interviews were based on "standard psychiatric intake interview, emphasizing active listening and thorough data gathering".[10] Patients in the intervention group talked to the pharmacist about six times and interviewed face to face on an "average of 1.6 office visits" during the 6 months. Both groups had mostly female patients, mean age was 61.1 ± 16.2 in the control group, and 59.9 ± 15.9 in the intervention group. Antidepressants used were mainly fluoxetine and paroxetine, with starting doses lower in the intervention group. It was noted that there was more switching of therapy in the intervention group. The primary outcome in this study was adherence to antidepressants and patient satisfaction. Adherence was tracked by fill history and patient satisfaction was evaluated through surveys. Refill records were reviewed, and a medication possession ratio (MPR) was calculated to ensure that patients were taking the medications as prescribed. The MPR was calculated by dividing the number of days-supply of antidepressants divided by 180 days (the length of the study). Adherence to antidepressants in the intervention group was statistically significant ($p < 0.005$), and 75% of patients referred were adherent and completed their six months of therapy. Satisfaction with pharmacy services was higher in some areas in the intervention group. There was a higher satisfaction in pharmacists' performance in areas of availability of advice, personal nature of the care, ability to listen and acknowledge concerns, information on how to take antidepressants, expectations, and how to deal with side effects. Evaluation of clinical outcomes resulted in a 12.1-point decrease in IDS scores at six weeks and a 14.6-point decrease at six months in the intervention group. Significant improvements from baseline were also reported in the clinical global impression (CGI) scores and Functional impairments scores; however, the results of the control group were not reported. Limitations of this study involved the absence of the results of clinical assessment in the control group, and the intervention group had mostly female patients with moderate-severe depression.

Valenstein *et al*. published a study that included patients from four Veteran Affairs facilities in Michigan, Illinois, and Massachusetts between the years 2002-2005.[11] The primary outcome of this randomized controlled clinical trial was to assess the effectiveness of pharmacy-based interventions on improving adherence to antipsychotics in patients with severe mental illness (SMI) for a 12-month period. Secondary outcomes were to evaluate clinical improvement, quality of life, and patients' satisfaction. The study enrolled 118 patients randomized into two groups, 60 to receive usual care versus 58 to receive Med Help interventions. The block randomization

method was used to group patients based on their level of adherence in the prior year measured by the medication possession ratio (MPR). This method excluded patients that seemed to be adherent, represented by an MPR > 0.8. Demographics were similar in both groups in terms of chronic medical conditions, except that 97% of patients included in the study were men with an average age of 49.9. The study included patients with schizophrenia, bipolar disorder, and substance use disorder. The medications prescribed for each group were similar and the most commonly prescribed antipsychotics were olanzapine and risperidone. The Meds-help intervention consisted of unit-of-use packaging, education sessions, refill reminders mailed two weeks before refill dates, and notification of physicians when patients failed to fill their antipsychotics within 7 to 10 days of fill date. During education sessions, the pharmacist performed a thorough review of patients' medications, explained treatment indications, explained unit-of-use packaging, and to use pillboxes temporarily when medication changes are made. The results showed an improved adherence to antipsychotics comparable to hypertensive and diabetic medications with a statistically significant medication possession ratio ($p < 0.0001$). Pharmacy technicians were utilized to track adherence, which provides an affordable option for pharmacies. However, a limitation of the study was it being underpowered to assess the improvement of clinical outcomes as a larger number of patients would be needed for that assessment.

Aljumah *et al*. conducted a randomized controlled clinical trial in Saudi Arabia in 2014, comparing patients receiving pharmacists' interventions to those receiving regular care in an outpatient clinic.[12] The study included 239 patients with moderate to severe major depressive disorder aged 18-60 years with no history of psychosis or bipolar disorder, followed up for 6 months. The intervention group involved a shared decision-making method (SDM), since adherence is an important part of the decision making about a patient's own health. Pharmacists conducted a 15-minute session at 3 months and a 10-minute session at 6 months. The severity of depression, adherence, quality of life, involvement in the decision, treatment satisfaction, and beliefs about antidepressants were assessed in the intervention group but not the control group. The tool used to assess the severity of depression was the Montgomery–Asberg depression rating scale (MADRS). The Morisky medication adherence scale (MMAS) was utilized to assess medication-taking habits for patients. The euro quality of life (EQ-5D) was used to assess quality of life for patients, which involves providing a description of health outcomes that gets assigned a specific value. To evaluate the extent of patient's involvement in the SDM, patient involvement in decision-making scale (OPTION) quantitative tool was used at the 3-month session in the intervention group only. Treatment satisfaction was measured using the self-report treatment satisfaction questionnaire for medication (TSQM 1.4) to evaluate the effectiveness and side effects of medications. Patients' medication-related beliefs were assessed using the Patients' Beliefs about medicine questionnaire (BMQ). Patients also reported their concerns about the harm of therapy. The results at 6 months showed a statistically significant 18% increase in adherence ($p < 0.0001$), 6% increase in satisfaction ($p < 0.0001$) and 8% decrease in concerns about the treatment ($p < 0.024$). Limitations of this study are the sample size that was not powered enough to detect a statistically significant effect in the severity of depression as well as a probable bias of patient's self-reporting.

Salazar-Ospina *et al*. published the effectiveness of the dader method (EMDADER-TAB) trial that was conducted in Columbia between the years 2011-2014.[13] The primary outcome of this randomized controlled clinical trial was the number of emergency room visits, hospitalization and unscheduled outpatient visits in patients with Bipolar I disorder (BD-I). The study also measured several secondary outcomes, including adherence assessed by measuring lithium and carbamazepine levels, quality of life, depression, mania, medication safety and patient satisfaction with the pharmaceutical services. The control group included 49 patients who received usual care of dispensing with written and verbal counseling, while the intervention group included 43 patients who received the Dader method of pharmaceutical care. The Dader method is an evaluation of the negative outcomes of therapy and solving drug-related problems during a 12-month period. The most frequent psychiatric treatments among the participating patients was the combination of atypical antipsychotics and mood stabilizers. Throughout the 12-month follow-up, pharmacists conducted weekly phone calls to assess patients' adherence and therapy effectiveness and informed physicians of beneficial therapy adjustments. Pharmacists also performed clinical assessments of mood, behavior, eating, and sleeping patterns. These close follow-ups allowed pharmacists to identify medication-related problems and promptly make changes that would improve clinical outcomes. The number of emergency room visits was 23 (82.1%) for the control groups versus 5 (17.9%) for the intervention group at the 1-year follow up. For clinical outcomes, there was a statistically significant improvement in the Hamilton depression rating scale in the intervention group compared to the usual care group ($p = 0.016$).

However, there was no statistically significant change in manic symptoms. Patients in the intervention group also showed a statistically significant improvement in the severity of symptoms ($p = 0.024$). Limitations of this study include possible bias from it being open-label, variable hospitalization history, and poor patients' insight of their illness. Furthermore, this study excluded patients with bipolar II disorders, first manic episodes, schizoaffective and personality disorders.

DISCUSSION

Most of the evidence collected from studies has shown that having pharmacists involved in patients' treatment plans positively impacted the rate of adherence to psychotropic medications for depression, schizophrenia, and bipolar disorders. Some of the studies did not show an improvement in the clinical outcomes alongside significantly improved adherence; these studies were not powered enough for this detection. Two studies showed statistically significant results in the improvement of symptoms and one study reported a significant decrease of emergency room visits for patients with bipolar I disorder. A limitation of this literature review is that it included older studies. However, search results were narrowed to controlled clinical trials that involved the primary outcome of adherence or improvement of clinical symptoms in patients with mental illness, which were very limited. Another limitation would be the different rating scales used in each study measuring symptoms' improvement, which may have produced inconsistent results.

Additionally, the number of patients included in these studies was relatively small, with varied background characteristics. The most common interventions made by the pharmacists included providing patients with individualized education on their medications in a regular manner and perform objective assessments to evaluate clinical improvement. Most pharmacists conducted their beneficial interventions through regular follow-ups consisting of face to face interviews or phone calls. This practice would provide reassurement to patients and a closer look at possible areas of therapeutic modifications. To implement pharmacists' interventions in the outpatient setting, phone calls and unite-dose-packaging are possible ways that would help with adherence issues. Some barriers to the implementation of mental health pharmacy services in the community setting include time and availability of clinical monitoring guidelines. Pharmacy software that would electronically flag patients who require pharmacists' counseling notify PCPs with medication changes, expand the role of pharmacy technicians, and mental health-focused continuous education courses can limit some of these barriers along with clear process improvements that ensure patients' privacy. Pharmacists in ambulatory care clinics or inpatient setting can be consulted to intervene and make recommendations with new prescriptions and change of therapy similar to anticoagulation consults. Implementing collaborative practice would give a greater opportunity to pharmacists to be involved in the decision-making and would further improve clinical outcomes. Pharmacists delivering realistic expectations of treatments can push patients to be part of their own health decision-making process. The significance of pharmacists' interventions can help come over the barriers to implementation and strengthen the pharmacist-patient relationship and trust. There would also be an expected reduction of costs associated with hospital admissions related to treatment failure.

CONCLUSION

Most pharmacists feel uncomfortable discussing mental illness with patients due to process barriers. However, pharmacists have the attitude and are equipped with skills to evaluate clinical symptoms of different psychiatric disorders as well as the knowledge on treatments necessary for the optimization of clinical outcomes. Pharmacists put education along with life-learned experiences into practice to have a positive impact on patients' wellbeing. Pharmacists are dependable, ethical, proactive team members who strive for patient-centered care. These skills require an understanding of the practice's rules, as well as the responsibilities associated with them, to satisfy every aspect involved in mental health appropriately. Evidence is significant for the effects of pharmacists' intervention on adherence rates to psychotropic medications. However, we need longer follow-ups on patients to witness the effects of improved adherence on their symptoms and quality of life.

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