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REVIEW

Strategies to improve medication adherence in patients with schizophrenia: the role of support services

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Abstract: The purpose of this review is to describe research over the past 10 years on the role of support services in promoting medication adherence in mental health consumers diagnosed with schizophrenia. A literature search was conducted using the terms "medication adherence," "schizophrenia," and "support services," using Medline, PubMed, and CINAHL. Reference lists from published studies were also reviewed to identify additional research studies. Twenty-two articles focused on support-service intervention studies, and these were selected for review. Available support-service interventions include adherence therapy, electronic reminders via text messages and telephones, cognitive–behavioral and motivational strategies, and financial incentives. Support-service intervention strategies need to be tailored to the specific needs of mental health consumers with schizophrenia. More research is needed to investigate effective support services to enhance long-term adherence and adherence to medications for medical illnesses in this population.

Keywords: schizophrenia, medication adherence, support services, therapy, interventions

Introduction

Adherence to pharmacological treatment is essential for alleviation of psychotic symptoms in schizophrenia. First-line antipsychotic medications are effective in approximately 70%–80% of persons diagnosed with schizophrenia (PWS); however, an estimated 50% of those who respond well to medications are nonadherent to their treatment regimen.[1] Wide variations have been observed in patterns of medication adherence among PWS. Nonadherence can range from patients who refuse to take medications due to lack of acceptance of the need for medication, to patients who recognize the need for medication and are committed to treatment but are nonadherent due to forgetfulness or financial constraints.[2] The consensus definition for adherence maintains that PWS can be considered adherent if they take more than 80% of prescribed medications; partial adherence is defined as taking 50% of prescribed medications.[3] Velligan and colleagues also report a consensus among experts that nonadherence can be defined as being off of medications for 1 week.[3]

Factors associated with medication nonadherence

As the definitions of adherence suggest, the decision to take medications in PWS is a complex phenomenon that involves multiple patient, environmental, provider, and medication-related factors. Patient-related factors include some demographic characteristics, such as newly starting treatment, younger age at onset of illness, alcohol dependence and other illicit substance use, homelessness, low levels of involvement

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in social activities, independent housing, and financial constraints with consequent inability to afford copayments for prescriptions.[4–9] Membership in a minority ethnic group also contributes to poor medication adherence; in a large study of 34,128 US veterans with schizophrenia, Valenstein et al[10] reported that the relative risk ratio for consistently poor adherence was 3.81 for African Americans compared to whites and 3.54 for Hispanics compared to whites. Lack of family support for adherence, or having no family, further contributes to nonadherence. Glick et al[11] and Moritz et al[12] observed that a positive attitude toward positive symptoms, particularly the perception of importance and power resulting from psychotic symptoms, also contributes to nonadherence. In addition, a study by Jónsdóttir et al[6] found that nonadherent PWS had significantly higher IQs, executive functioning, memory, and verbal learning/fluency compared to fully adherent PWS.

Perceptions about illness and medications are very important factors that influence adherence. For example, adherence is higher among PWS who have insight and an awareness of the need to take medications to alleviate symptoms and avoid hospitalization.[7,13–15] In addition, favorable attitudes toward mediations and the expectation that medications are effective in reducing symptoms contribute to adherence.[15,16] Intolerable side effects are a major reason for discontinuing medications.[12,15] For example, side effects associated with typical antipsychotics, such as extrapyramidal symptoms, sedation, and elevated prolactin levels, are particularly problematic. Metabolic side effects of atypical antipsychotics, including weight gain, further contribute to lack of adherence.[17] However, some research suggests that recognition of the benefits of medications in alleviating troublesome psychotic symptoms improves willingness to tolerate the side-effect burden for the sake of mental wellness.[18] Similarly, Liu-Seifert et al[19] compared adherence among 1,103 people treated with olanzapine and 1,090 people treated with other atypical antipsychotic medications (risperidone, quetiapine, ziprasidone, or aripiprazole). Findings suggested that an improvement in the positive symptom rating subscale of the Positive and Negative Syndrome Scale was the strongest predictor of treatment adherence, regardless of the medication that was prescribed.

Much research supports the critical need for a strong and positive therapeutic relationship in the promotion of medication adherence.[20,21] Misdrahi et al[7] found that therapeutic alliance was significantly associated with medication adherence (r=0.663) among 38 PWS. Similarly, Dassa et al[16] found that nonadherence to medications increased with a low level of therapeutic alliance (odds ratio =0.45, 95% confidence interval =0.32–0.64) among 291 PWS. Research also suggests that patients value support from prescribers regarding medication, particularly when prescribers provided accurate information about potential side effects of medication, expressed understanding of the patient perspective, and listened to patients' concerns about the medications. In addition, Day et al[20] reported that the experience of admission to the hospital is an important factor that influences willingness to take medications; the perception of coercion, lack of a voice in treatment decisions, and negative pressure to enter the hospital are all associated with nonadherence to psychiatric medications.

Adherence to medications for medical illnesses

High rates of cardiometabolic problems among PWS have prompted clinicians to focus on adherence to treatment for medical illnesses in this population. Research investigating adherence to medical care has yielded varying results. Pratt et al[22] in a study of 72 participants with serious mental illnesses, reported adherence rates of 57% for psychiatric medications and 64% for medications for medical illnesses. Hansen et al[23] in a study of 87,015 PWS with comorbid medical illnesses, found that adherence to medications for hypertension, hyperlipidemia, and diabetes was significantly greater among those who were adherent to antipsychotic medications, with an adjusted odds ratio of 6.9. In a study of 11,454 US veterans, Kreyenbuhl et al[24] found poor adherence to medications for Type 2 diabetes mellitus (T2DM) in 43% of veterans with schizophrenia and T2DM, compared to poor adherence rates among 52% of veterans with T2DM and no mental illness. Similarly, Nelson et al[25] found that gaps in filled prescriptions for antihyperlipidemic medications were 44 days for veterans diagnosed with schizophrenia and T2DM, compared to 62 days for veterans with T2DM and no mental illness.

Piette et al[26] noted that in a study of 1,686 veterans diagnosed with schizophrenia and comorbid diabetes and hypertension, differential rates of adherence depended on the type of medication prescribed to participants; findings suggest that treatment with antihypertensive and diabetes medications was associated with an increased risk for low adherence compared to antipsychotic medications. Dolder et al[27] found that rates of adherence to antihypertensive agents in 89 veterans with psychotic disorders were similar to rates in 89 randomly selected, age-matched veterans without psychotic disorders; however, blood pressure control was significantly poorer over a 1-year period in the participants

with psychotic disorders. In contrast, Dolder et al[28] found that among 76 middle-aged and older veterans with schizophrenia, 12-month adherence rates ranged from 52%–64% for antipsychotic medications and medications to treat hypertension, diabetes, and hyperlipidemia. Beebe et al[29] in a study that compared the effectiveness of a telephone intervention to improve medication adherence (n=15) to usual care (n=14), found that average adherence rates to medications for medical illnesses was 33% for the intervention group and 22% for the treatment-as-usual (TAU) group throughout the duration of the study.

Consequences of nonadherence

Partial or complete lack of adherence to medications is associated with several negative outcomes in PWS.[8,30] Medication nonadherence is associated with an increased risk for relapse of psychosis, persistent symptoms, and suicide attempts.[8,31] Among PWS experiencing a first episode of psychosis, symptom recurrence rates are an average of 77% within 1 year of stopping medications, and over 90% within 2 years of stopping medications.[30] Bodén et al[32] found that nonadherence to medications during the first week after discharge from an inpatient hospitalization was associated with a high risk for rehospitalization within 1 month of discharge. Length of hospital stay is also extended due to nonadherence.[30] Finally, Gilmer et al[5] found that average hospital costs in nonadherent inpatients were three times higher than costs for adherent inpatients, although pharmacy costs were higher among adherent compared to nonadherent inpatients.

Current strategies to improve adherence

Several support services are available to address specific problems with adherence.[33] For example, therapeutic support services provide counseling, with the goal of identifying and modifying cognitive and motivational barriers to adherence. Cognitive-behavioral therapy (CBT) addresses inaccurate beliefs and negative perceptions about medications and the need for treatment.[3] CBT is often used in conjunction with motivational interviewing (MI), which seeks to resolve ambivalence about taking medications and addresses perceptions about the importance of taking medications and confidence in the ability to adhere to a medication regimen.[34] Cognitive adaption training provides tailored environmental cues and supports to compensate for cognitive impairments that cause memory problems; these include alarms, pillboxes, activity checklists, and organization of personal belongings.[33] Adherence/compliance therapy is a multifaceted approach that includes CBT, psychoeducation, and MI.[3] Support

services can also address logistic barriers to adherence, such as arranging transportation to pharmacies and obtaining insurance benefits.[3]

This review summarizes research from the past 10 years on interventions that examined the role of support services in promoting adherence to psychiatric medications and medications for medical illnesses among PWS. A literature search was conducted using the terms "medication adherence," "schizophrenia," and "support services" and "interventions" using Medline, PubMed, and CINAHL. Reference lists from published studies were also reviewed to identify additional research studies. A total of 22 articles were located using these search terms and are included in this review.

Results

Findings from this literature review are displayed in Tables 1–4. Of the 22 studies reviewed, eleven significantly improved adherence to medications in the study samples, and five did not result in significant improvements.

Support service interventions
Family and/or clinician support/education

Seven intervention studies examined the effectiveness of family and/or clinician support and education (Table 1).[35–41] Two family studies showed promising findings. Farooq et al[37] implemented an intervention to train family members to be key care supervisors of medication adherence (coupled with free medications). Findings indicated that medication adherence was significantly increased in the intervention group.[37] Kopelowicz et al[39] found that culturally adapted multifamily groups tailored to Spanish-speaking Mexican Americans, who had three individual and family psychotherapy sessions, a 1-day family workshop, and 24 family group sessions that focused on attitudes, beliefs, planned behaviors, and subjective norms, had increased adherence compared to multifamily groups only or TAU.

Interventions involving clinician support and education yielded varying results. Sajatovic et al[41] examined the effectiveness of a psychosocial/psychoeducational customized adherence enhancement program for homeless people taking long-acting antipsychotic injections (LAIs), which focused on medication routines, communicating with clinicians, and managing adherence in the presence of substance abuse. The customized adherence enhancement program was associated with good adherence to LAIs in 76% of participants. Oral medication adherence improved to only 10% missed medication doses postintervention compared to 46% missed doses prestudy. However, only four out of 30 continued taking

Table 1 Family and/or clinician educational support

Citation	Anderson et al[35]	Byerly et al[36]	Farooq et al[37]	Gray et al[38]	Kopelowicz et al[39]	Mittal et al[40]	Sajatovic et al[41]
Design type	RCT	Quasi-experimental	RCT	RCT	3-armed RCT	RCT	Prospective, noncontrolled trial
Intervention description	AT – weekly sessions for 8 weeks, 20–60 minutes Focus: problem solving, medication timeline, ambivalence, medication beliefs/concerns, using medications in the future	Compliance therapy 4–6 sessions, 30–60 minutes each Focus: Illness history, medication beliefs/ understanding, treatment ambivalence, stigma	STOPS – family member as key care supervisor One session to train key care supervisor Free medications for all participants in STOPS group and for those in the TAU group who could not afford medications	AT – weekly sessions for 8 weeks Focus: problem solving, medication timeline, ambivalence, medication beliefs/ concerns, using medications in the future Health education – weekly sessions for 8 weeks	Culturally adapted multifamily group Tailored to Spanish-speaking Mexican-Americans (MFG-Ad) compared to MFG-S and TAU 3 individual and family sessions One-day family workshop MFG-Ad: 24 family group sessions, focus: attitudes, beliefs, planned behaviors MFG-S: no focus on attitudes, beliefs, planned behaviors	AAI – 9 sessions: Face to face daily ×3 Face to face weekly ×3 Telephone monthly ×3 Education, skills training, alliance building Focus on medication management, communication, building relationships with health care providers	CAE, a psychosocial/ psychoeducational program about medication use plus haloperidol decanoate-LAI = CAE-L administered over 6 months
Data collection time points	Baseline Postintervention	Monthly – 3 months preintervention to 6 months postintervention	Baseline, 3 months, 6 months, 12 months	Baseline and 52 weeks	Baseline, 4 months, 8 months, 12 months, 18 months, 24 months	Baseline, 4 weeks, and 4 months	Treatment = baseline, 13, and 25 weeks follow-up; Posttreatment follow-up =9 and 12 months
Sample	AT =12 TAU =14	n=30 No control group	STOPS=55 TAU =55	AT =204 HE =205	MFG-Ad =64 MFG =53 TAU =57	AAI =22 TAU =18	n=30
Measures	ATSAT LUNSERS PANSS PETiT	MEMS PANSS DAI	PANSS GAF Adherence to Medication Scale	MOS SF-36 SAI-E MAQ BPRS-E	Treatment Compliance Interview	Self/caregiver adherence report Pharmacy refill records PANSS QWBS CDS BAS AIMS DAI ITAS I4-Q	Primary = medication adherence and housing status via self-reports: TRQ MRS ATMSQ DAI Psychiatric symptoms: BPRS, PANSS, CGI Functioning: SOFAS

Findings						
No significant improvements in medication adherence or psychiatric symptoms	Adherence significantly increased 1 month after intervention, declined by 1.4% per month for remaining months No change in symptoms, insight, attitudes to taking medications	STOPS: significant reduction in PANSS scores, positive/general symptoms, significant improvement in GAF Significantly higher adherence in the STOPS group compared to TAU at 3 months, 6 months, and 12 months (67% vs 45% at 1 year follow-up, $P<0.02$)	No significant difference in medication adherence and quality of life between AT and HE groups	MFG-Ad had increased adherence compared to MFG-S and TAU Longer time to first hospitalization Less likely to be hospitalized	65% of AAI group adherent after 4 months 55.6% TAU group adherent No significant difference	CAE-L associated with good adherence to LAI at 6 months =76%, Overall oral medication adherence: 46% missed prior to study versus 10% at 6 months ($P=0.03$) Only 4 continued to take LAI 6 months poststudy Significant improvements in psychiatric symptoms ($P<0.001$) and functioning ($P<0.001$)

Abbreviations: 14-Q, 14-Point Questionnaire; AAI, antipsychotic adherence intervention; AIMS, Abnormal Involuntary Movement Scale; AT, adherence therapy; ATMSQ, Attitude Towards Mood Stabilizer Questionnaire; ATSAT, Adherence Therapy Patient Satisfaction Questionnaire; BAS, Barnes Akathisia Scale; BPRS-E, Brief Psychiatric Rating Scale-Expanded; CAE, customized adherence enhancement program; CAE-L, customized adherence enhancement plus long-acting injectable antipsychotic; CDS, Calgary Depression Scale; CGI, Clinical Global Impressions Scale; DAI, Drug Attitude Inventory; GAF, Global Assesment of Functioning; HE, health education; ITAS, Insight and Treatment Attitude Scale; L or LAI, long-acting injection; LUNSERS, Liverpool University Neuroleptic Side Effect Rating Scale; MAQ, Medication Adherence Questionnaire; MEMS, Medication Event Monitoring Scale; MFG, multifamily group; MFG-Ad, Multifamily Group-Adherence; MFG-S, Multifamily Group – Standard; MOS SF-36, Medical Outcomes Survey 36-item short form questionnaire; MRS, Morisky Rating Scale; PANSS, Positive and Negative Syndrome Scale; PETIT, Personal Evaluation of Transitions in Treatment; QWBS, Quality of Well-Being Scale; RCT, randomized controlled trial; SAI-E, Schedule for the Assessment of Insight – Expanded Version; SOFAS, Social and Occupational Functioning Assessment Scale; STOPS, supervised treatment in outpatients for schizophrenia; TAU, treatment as usual; TRQ, Tablet Routine Questionnaire.

LAI 6 months poststudy. In contrast, Byerly et al[36] found that adherence did not increase after four to six sessions of compliance therapy that focused on illness history, and medication beliefs, understanding, ambivalence, and stigma of treatment. Anderson et al[35] found no significant improvements in medication adherence following eight weekly sessions of adherence therapy that included problem solving, exploration of ambivalence toward medication beliefs, concerns, and using medications in the future. Similarly, Gray et al[38] found that there was no significant difference in adherence between adherence therapy that included eight weekly sessions about problem solving, medication timeline, ambivalence, beliefs, and concerns about using them in the future versus eight weekly health education sessions. Mittal et al[40] found that there was no significant difference between antipsychotic adherence therapy versus TAU following nine weekly sessions of daily, then weekly, face-to-face and telephone education, alliance building, and skills training in veterans aged 40 years and older.

Technology-based services

A variety of electronics-based strategies were studied, including text messages, phone reminders, pill counters, electronic pill dispensers, and a computerized program symptom alert system (Table 2).[29,42–46] Pijnenborg et al[44] used text messages in an intervention to examine the effectiveness of six weekly group sessions focusing on coping with cognitive impairment associated with schizophrenia. The study also involved instructions on how to send/receive text messages, including a total of 7 weeks of receiving text messages as a reminder to adhere to medications and other self-chosen treatment goals. Adherence to medications in the intervention group was 57% at baseline and 65% during the intervention, but fell to 48% at follow-up when text prompts were no longer being received. Granholm et al[42] found that sending three sets of four text messages about medication adherence, socialization, and auditory hallucinations to people with schizophrenia significantly improved medication adherence for those living independently. Similarly, Montes et al[43] found that after sending daily short-message-service reminders or texts for 3 months as a prompt to take medications, there was a significantly reduced score on the Medication Adherence Questionnaire (a four-item self-report of reasons for medication adherence failure, with a low score indicating better adherence) in the intervention group at 3 months, and at 6 months adherence was maintained.

Beebe et al[29] found that study participants who received weekly telephone call reminders to take their medications

Table 2 Electronic devices

Citation	Beebe et al[29]	Granholm et al[42]	Montes et al[43]	Pijnenborg et al[44]	Španiel et al[45]	Stip et al[46]
Design type	RCT	Quasi-experimental; pilot study	RCT open-label, multicenter trial	Quasi-experimental waiting list controlled trial; random assignment	RCT 1-year prospective, parallel-group, double-blind study	RCT
Intervention description	TIPS Weekly telephone calls for 3 months Focus: problem solving, coping strategies, reminders to take medications	3 sets of 4 text messages sent via mobile phone, 6 days per week for 12 weeks – CBT format Focus: medication adherence, socialization, AH	Intervention group = daily reminders for 3 months via text message (SMS) to take their medication Control group = no text reminders to take medications	6 weekly psychoeducation group sessions with 5–7 patients Weeks 1–2 = baseline goals set (A1) 3 weeks = reminder texts about adherence + usual care = (B) Last 3 weeks during intervention = daily goals achieved 3 weeks postintervention = number of daily goals remeasured =(A2)	Text message sent via computer program: ITAREPS 1 time/week Active group prodromal psychotic symptoms via weekly ALERT emails PIRE = triggered clinician to increase antipsychotic medication dose Active group = used ITAREPS and EWSQ-10P/ EWSQ-10FM + usual treatment Control group = usual treatment	3 visits: baseline, 6 weeks, and 8 weeks to measure impact of DoPill's® (electronic pill dispenser) impact on medication adherence and psychiatric symptoms

Data collection time points	Baseline and monthly for 3 months	Baseline and 12 weeks	Baseline, 3 months, and 6-months	Intervention group: A1 + B + A2: A1 = baseline phase, B = intervention phase, A2 = follow-up phase Controls: A1 + A0 + B + A2 (A0 = extra baseline condition to control for passing time)	Baseline, 6 months, and 12 months (end of study)	Baseline, 6 weeks, and 8 weeks
Sample	TIPS =15 TAU =14	n=55	SMS =100 patients Controls =154 patients	n=62	Intervention =75 Controls =71	Experimental group =26 Control group =21 47 total completed study
Measures	Pill counts	PANSS BDI-II ILSS	MAQ DAI SUMD EQ-5D CGI-SCH CGI-SI-DC	PANSS SFS SCMTS	CGI-S and CGI-I Hayward MCRS GAF PIRE detected by ITAREPS	BARS PANSS DoPill® electronic/digital report (frequency) Antipsychotic Adherence Ratio
Findings	TIPS: 80% adherence to psychiatric medications; 33% adherence to nonpsychiatric medications TAU: 60.1% adherence to psychiatric medications; 22% adherence to nonpsychiatric medications Significantly higher adherence in TIPS group vs TAU group	Significant improvement in medication adherence for those living independently; improved social functioning; reduced severity of AH	Significantly reduced MAQ score with SMS reminders vs controls at 3 months (25% versus 17.5%) at 6 months, maintained MAQ score change from baseline	Overall % of goal-achievement =47% across patients, (SD =27.9%) and increased with text prompting =62% (SD =20.1%, returned to baseline levels without prompts =40% (SD =31.7%); Medication adherence = 57% at baseline (A1), 65% at intervention phase (B), and 48% at follow-up (A2)	No significant difference in medication adherence between groups	46% non-adherent; Baseline adherent patients had significantly > adherence vs non-adherent patients over 6-weeks via BARS measures; ie, Mean AAR 67% after 6-weeks; Proportion of patients with <70% and <90% AAR =46% and 54%

Abbreviations: AAR, antipsychotic adherence ratio; AH, auditory hallucinations; BARS, Brief Adherence Rating Scale; BDI-II, Beck Depression Inventory-Second Edition; CBT, cognitive–behavioral therapy; CGI-I, Clinical Global Impression Scale-Improvement; CGI-S, Clinical Global Impression Scale-Severity; CGI-SCH, Clinical Global Impression Scale-Schizophrenia; CGI-SI-DC, Clinical Global Impression-Severity of Illness and Degree of Change; CL, confidence limit; DAI, Drug Attitude Inventory; EQ-5D, EuroQol; EWSQ-10FM, 10-item Early Warning Signs Questionnaire (Family Member); EWSQ-10P, 10-item Early Warning Signs Questionnaire (Patient); GAF, Global Assessment of Functioning; ILSS, Independent Living Skills Survey; ITAREPS, Information Technology-Aided Program of Relapse Prevention in Schizophrenia; MAQ, Medication Adherence Questionnaire; MCRS, Medication Compliance Rating Scale; PANSS, Positive and Negative Syndrome Scale; PIRE, pharmacological intervention requiring event; RCT, randomized controlled trial; SCMTS, Short Client Motivation for Therapy Scale; SD, standard deviation; SFS, Social Functioning Scale; SMS, short message service; SUMD, Scale to Assess Unawareness of Mental Disorder; TAU, treatment as usual; TIPS, telephone intervention problem-solving.

Table 3 Motivational interviewing

Citation	Barkhof et al[47]	Hudson et al[48]	Maneesakorn et al[49]	Staring et al[50]
Design type			RCT	RCT
Intervention description	Motivational interviewing versus health education 5–8 sessions over 26 weeks	Veterans Affairs practice guideline implementation RN counseling/problem solving Clinical interview – baseline and every visit At least every 6 weeks for 6 months – adherence barriers and strategies	AT – 8 weekly sessions Focus: medication problem solving, ambivalence, beliefs, concerns about taking medications, using medications in the future	Intervention group/TAT = MI, medication optimization, behavioral training Control group = TAU
Data collection time points	Baseline, 26 weeks, 6 months	Baseline and 6 months	Baseline and 9 weeks	Baseline and 6 months
Sample	MI =55 HE =59	Enhanced/RN counseling =173 Standard =176	AT =14 TAU =14	TAT =54 TAU =55
Measures	PANSS MAQ LCS DAI	PANSS BARS Schizophrenia Outcomes Module Self-report/medical record review for adherence	PANSS GAF DAI-30 SWAM LUNSERS	SES MAQ DAI CRS PANSS EQ-5D Birchwood Insight Scale
Findings	No significant differences in medication adherence between MI and HE; reduced hospitalizations for female patients in the MI group	Veterans with enhanced guideline/RN counseling significantly more likely to be adherent at 6-month follow-up Adherence at 6 months significantly associated with adherence at baseline, female sex, and negative baseline akathisia	AT group: significant improvement in PANSS scores, positive symptoms, attitudes toward medications, satisfaction with medications compared to TAU	TAT = significantly improved service engagement and medication adherence compared to TAU TAT effect less at 6-month follow-up but remained significant for medication adherence No improvement in symptoms or quality of life

Abbreviations: AT, adherence therapy; BARS, Brief Adherence Rating Scale; CRS, Compliance Rating Scale; DAI, Drug Attitude Inventory; DAI-30, Hogan Drug Attitude Inventory; EQ-5D, EuroQol; GAF, Global Assessment of Functioning; HE, health education; LCS, Life Chart Schedule; LUNSERS, Liverpool University Neuroleptic Side Effect Rating Scale; MAQ, Medication Adherence Questionnaire; MI, motivational interviewing; PANSS, Positive and Negative Syndrome Scale; RCT, randomized controlled trial; RN, registered nurse; SES, Service Engagement Scale; SWAM, Satisfaction with Antipsychotic Medication Scale; TAT, treatment adherence therapy; TAU, treatment as usual.

Table 4 Miscellaneous support services

Citation	Morken et al[51]	Priebe et al[52]	Valenstein et al[53]	Velligan et al[54]	Velligan et al[33]
Design type	RCT	RCT with cluster randomization controlled trial of treatment teams	RCT with block-randomization of patients (experimental without double-blind)	3-armed RCT	3-armed RCT
Intervention description	IT =2 years of assertive outreach community treatment, family psychoeducation, social skills training/CBT	Patients on intervention teams who adhered ≤75% of the time 4 months prior to screening received financial incentive of $22/clinic visit to receive prescribed long-acting antipsychotic injection	Intervention: Meds-Help = unit-dose medication packaging medication education	Pharm-CAT – tailored environmental supports and weekly home visits Med e-Monitor – prompts from an electronic device in the patient's home; telephone contacts TAU	Full-CAT – tailored environmental supports for independent living skills, social/role performance, medication adherence Pharm-CAT – tailored environmental supports for medication and appointment adherence only TAU
Data collection time points	Baseline, 12 months, 24 months	Baseline to 12-month endpoint	12 months prior to enrollment (baseline), 0–6 months, and 6–12 months after enrollment	Baseline, 3 months, 6 months, 9 months	Baseline, 3 months, 6 months, 9 months, 12 months, 15 months
Sample	IT =30 Control =20	Intervention =78, control =63	Meds-Help =58 TAU =60	Pharm-CAT =46 Med e-Monitor =46 TAU =45	Full-CAT =34 Pharm-CAT =32 TAU =29
Measures	Medication Adherence (self, family and clinician reports) Camberwell Family Interview BPRS	Medication adherence CGI DIALOG scale Satisfaction with medication	Primary: MPR Secondary: PANSS QWBS CSQ	Medication adherence SCID BPRS SOFAS Service use	SCID Pill counts BPRS SOFAS Relapse Score
Findings	No significant differences in medication adherence between IT and ST Men more non-adherent than women	Modest financial incentives improve adherence to LAI 12-month trial adherence: intervention group =85%, controls =71% Secondary outcome adherence of ≥95%: intervention group =28% controls =5%	MPRs = Meds-Help group had significantly > MPRs at 6 months (Meds-Help MPR 0.91, UC MPR 0.64) and 12 months Meds-Help MPR 0.82, UC 0.62 (*P*<0.0001)	Medication adherence – Pharm-CAT =90% Med e-Monitor =91% TAU =73% Both Pharm-CAT and Med e-Monitor significantly higher than TAU	Medication adherence significantly higher in Full-CAT and Pharm-CAT groups compared to TAU; remained significantly higher after home visits stopped

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impressions Scale; CBT, cognitive–behavioral therapy; CSQ, Client Satisfaction Questionnaire; Full-CAT, full cognitive adaptation training; IT, integrated treatment; LAI, long-acting injectable; MPR, medication possession ratio; PANSS, Positive and Negative Syndrome Scale; Pharm-CAT, cognitive adaptation training with medication education; QWBS, Quality of Well-Being Scale; RCT, randomized controlled trial; SCID, Structured Clinical Interview for Diagnosis; SOFAS, Social and Occupational Functioning Assessment Scale; ST, standard treatment; TAU, treatment as usual; UC, usual care.

for psychiatric and medical conditions over 3 months had significantly higher adherence compared to TAU controls. Those in the intervention group were 80% adherent to psychiatric medications and 33% adherent to medications for medical conditions.

Stip et al[46] found that after 8 weeks of using an electronic pill counter to assess medication adherence, 46% were nonadherent. The mean antipsychotic adherence ratio was 67% after 6 weeks. Participants who were adherent at baseline had significantly greater adherence versus those who were nonadherent at baseline. Španiel et al[45] found that after 1 year of computer prompts to clinicians to increase antipsychotic medication doses when participants reported psychotic symptoms (via an electronic message), there was no significant difference in medication adherence in the intervention group compared to controls.

Motivational interviewing interventions

MI was used in conjunction treatment adherence therapy (TAT) and problem solving approaches (Table 3).[47–50] Barkhof et al[47] found that there were no significant differences in medication adherence after 26-week and 6-month interventions of MI versus health education. Staring et al[50] examined the effectiveness of 6 months of TAT, which includes MI, medication optimization, and behavioral training, and found that TAT significantly improved medication adherence. Findings also indicated that, despite a decrease in effectiveness at the 6-month follow-up, adherence in the intervention group remained significantly higher than in the TAU group.

Hudson et al[48] found that clinical interviews with a registered nurse who asked people to identify barriers to adherence and tailored strategies to overcome them via problem solving at each clinic visit (minimum of every 6 weeks) for 6 months significantly increased adherence at the 6-month follow-up. Adherence at 6 months was significantly associated with baseline adherence, female sex, and no akathisia at baseline. Maneesakorn et al[49] examined the effectiveness of eight weekly sessions of adherence therapy which focused on medication problem-solving, beliefs/attitudes/ambivalence toward taking medications, and taking medications in the future. Findings indicated that the participants in the adherence-therapy group showed significant improvements in positive symptoms, attitudes toward medications, and satisfaction with medications. In this study, medication adherence was not used as a primary outcome measure; the authors noted that the outcomes of symptom reduction and medication attitudes and satisfaction, rather than adherence, are indicators of the potential health gain due to the intervention.[49]

Other support service interventions

A variety of other support interventions were examined (Table 4);[33,51–54] these included integrated treatment,[51] financial incentives,[52] a pharmacy-based intervention,[53] and environmental supports.[33,54] Morken et al[51] found that a multifaceted program that implemented CBT along with assertive outreach community treatment, family psychoeducation, and social skills training, did not significantly improve medication adherence compared to TAU. Priebe et al[52] found that modest financial incentives, in the amount of $22 per clinic visit, to receive an LAI during a 12-month trial increased adherence from <75% at baseline to 85%, compared to 71% among controls. Greater than 95% adherence was seen in 28% of the intervention group, compared to 5% in the control group. Valenstein et al found that, compared to controls, patients using a pharmacy-based intervention that included unit-dose prescriptions of medications for psychiatric and medical conditions, medication education in packaging, and refill reminders mailed 2 weeks in advance for 6 and 12 months had significantly increased medication possession ratios (MPR, a measure that includes self-reports of adherence combined with pill counts and serum labs indicating presence of medication).[53]

Environmental supports involved the use of home visits and adaptation of participants' home environment to incorporate cues as reminders to adhere to treatment. Velligan et al[54] found that home visits with full cognitive adaptation training, a tailored environmental support system aimed at improving independent living skills, and cognitive adaptation training with medication education, a tailored environmental support system for medication and appointment adherence, significantly improved medication adherence in both groups compared to the TAU group, and this difference remained significant after home visits stopped.

Discussion

Findings suggest that the utility of available support services to enhance medication adherence depend on a variety of factors, such as the PWS's attitudes toward treatment, perceptions of the need to take medications, and specific environmental and cognitive characteristics. Technological supports, such as mobile phone text message reminders, can be beneficial to PWS who are committed to medication adherence and are occasionally nonadherent due to forgetfulness. Similarly, interventions that focus on environmental cues to

remind PWS to take their medications can be very helpful in patients with memory problems.[54] In contrast, findings from this review suggest that therapeutic support services are more appropriate to PWS who are ambivalent toward taking medications and or deny the need to take medications. The most effective support service interventions are tailored to the specific needs of PWS, use a problem-solving approach to identify barriers to taking medications, and address ambivalence that PWS have toward committing to a life-long medication regimen.

Results of this literature review should be regarded with caution due to some limitations in the study designs. Adherence to psychiatric medications may depend on the participants' age, financial constraints/affordability of medications,[9] adverse effects, severity of psychiatric symptoms, duration of illness, side effects, and therapeutic response. Younger age is a noteworthy predictor of nonadherence.[4] However, in the studies reviewed here, only two focused on younger participants. One included family members as caregivers,[39] in which the mean age of participants was 24.6±8.3 years, and one included participants with recent onset of symptoms;[31] the mean age of participants in this study was 25.1±4.5 years. In the remaining studies, the mean ages of participants ranged from approximately 30–50 years, which limits generalizability to other age groups. Problems with medication adherence due to financial constraints and affordability of medications were not addressed in these studies, which is a noteworthy gap that warrants further research.

Medication side effects are known contributors to poor medication adherence among PWS.[17] However, only three studies in this review included a measure of side effects as an outcome variable. Maneesakorn et al[49] found reduced scores on the Liverpool University Neuroleptic Side Effect Rating Scale in the TAU group at a 9-week follow-up; the authors attribute this to the higher number of participants who were prescribed atypical antipsychotics in the TAU group. Hudson et al[48] found greater adherence associated with negative baseline akathisia score. Finally, Sajatovic et al[41] reported that in an adherence study that included LAIs, 40% reported akathisia, but no significant changes were seen in body mass index or total cholesterol. Findings from this review suggest that further research is warranted to examine the degree to which adverse or side effects of the more frequently used atypical antipsychotics influence medication adherence, particularly related to the emergence of obesity and cardiovascular/metabolic problems.

Severity of psychotic symptoms and level of cognitive functioning can also influence medication adherence. In the studies included in this review, all but four assessed symptom severity at the outset of the studies. Rating measures included the Positive and Negative Syndrome Scale, the Clinical Global Impressions Scale, and the Brief Psychiatric Rating Scale. Across all studies that measured symptoms, baseline symptom severity scores ranged from very mildly to moderately ill. It is likely that PWS who experience very severe symptoms are excluded from medication adherence research because very severe symptoms prevent them from providing informed consent for participation. Consequently, research on medication adherence has limited generalizability toward PWS with severe psychotic symptoms, and unfortunately PWS who refuse or are unable to participate are most in need of support services to improve adherence. In addition, participants' treatment response was minimal in many of the studies, as evidenced by nonsignificant changes in symptom severity scores at the conclusion of the studies.[33,35,36,42,43,45,53]

Several authors also reported that PWS who refused to participate in the studies had considerable deficits in cognitive functioning. Limitations on eligibility based on cognitive functioning tended to limit the sample sizes, which ranged from 25–409; the majority of studies had less than 100 participants. Several authors pointed out that eligibility based on cognitive functioning and symptoms resulted in selection bias, which increased the likelihood that participants had higher levels of functioning.[49]

Very little longitudinal research has been conducted on medication adherence over the lifetime trajectory of illness among PWS; the maximum duration of time included in an adherence study was 4 years.[53] Patterns of adherence may be unstable over time; Valenstein et al[10] investigated patterns of medication adherence, measured by MPR over a 4 year period among 34,128 veterans with schizophrenia, and the findings suggested that over 60% of veterans had adherence problems at some point during the 4 year period. Findings also indicated that over a 4 year period, about 18% had consistently poor adherence, defined as MPRs <0.8 in all 4 years; 43% had inconsistent adherence, defined as MPRs ≥0.8 in some years in the observation period, and 39% had consistently good adherence, defined as MPRs ≥0.8 in all 4 years.

Very few reviewed studies focused on the effectiveness of support services in improving adherence to medications in the treatment of medical illnesses. Furthermore, it is important to note that in the study conducted by Beebe et al[29] the telephone intervention problem-solving intervention improved adherence to psychiatric medications but not to medications for medical illnesses. Problems with adherence to medications for medical illnesses are by no means unique

to PWS. Rates of medication nonadherence are about 50% in the general population,[55] which is essentially identical to rates of nonadherence to psychiatric medications among PWS.[1] Low adherence to medications in the general population has been attributed to poor health literacy, intolerable side effects, and unaffordable copayments.[55] In addition, people in the United States who are diagnosed with multiple chronic medical illnesses often receive fragmented care from several different providers, which results in complex medical regimens consisting of multiple medications.[55]

PWS who have complex comorbid medical illnesses likely experience barriers similar to those found in the general population, particularly related to fragmented care.[26] A supportive therapeutic alliance has been shown to promote medication adherence in PWS, yet Piette et al[26] have observed that fragmented and poorly coordinated medical care from multiple providers in different treatment settings is a considerable barrier to the development of a trusting relationship between patients and provider. In addition, PWS have an even greater risk for nonadherence compared to the general population due to problems with motivation and cognitive impairments that interfere with memory, attention, problem-solving, and health-related decision making.[56]

Adherence to medications that treat psychiatric and medical illnesses is essential for PWS to achieve recovery goals and optimize overall wellness, yet ongoing research strongly suggests that physical health status and overall wellness in this population are far from ideal. PWS suffer from higher-than-average rates of comorbid chronic medical illnesses and experience worse outcomes due to these illnesses compared to the general population, including higher rates of emergency hospital admissions, longer length of hospitalization for medical problems, and shorter length of survival.[57–59] Much attention has been focused on the recent report that the life expectancy of PWS being served in the US state mental health system is 25 years shorter than that of the general population.[60] These appalling morbidity and mortality statistics illustrate health disparities that are increasingly untenable to patients, clinicians, policy makers, and family members.[61–63] A comprehensive initiative to reduce health disparities, integrate physical and mental health care, and improve mental and physical health status would need to address multiple barriers to effective health care among PWS, their providers, and health care delivery systems; the development of more-effective support services to improve adherence to medications for psychiatric and medical illnesses is foundational in this effort.[64]

Implications for practice

As this review illustrates, several strategies are available to prescribers to address medication adherence issues among PWS. The essential first step is the establishment of a trusting therapeutic relationship with the patient.[7,16,20,21] In the event that inpatient hospitalization is needed, PWS should be included in treatment decisions as much as possible.[20] Prior to implementation of support services, it is recommended that prescribers work with the patient to conduct a root-cause analysis of reasons for nonadherence; implementation would target specific support strategies to address them. It is recommended that prescribers address adherence to psychiatric medications as a priority and then address adherence to medications for medical illnesses as a secondary goal, since PWS have reported that stable psychiatric symptoms are an essential precursor to effective management of medical illnesses.[56,65]

Prescribers can also use cognitive strategies to link medication adherence to the patient's treatment goals, such as staying out of the hospital, living independently, maintaining normal glycemic control, or returning to work or school, as recommended in the Medication Treatment, Evaluation and Management evidence-based practice.[66] Finally, prescribers can promote optimal medication adherence by regularly including PWS in decisions about medications and assessing patient knowledge and attitudes about medications throughout the provision of support services.[66]

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