Pillbox Intervention Fidelity in Medication Adherence Research: A Systematic Review

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Abstract

Background: Pillboxes are widely available, but optimizing pillboxes in self-management interventions requires an understanding of important intervention components.

Purpose: To review components of intervention design, interventionist training, delivery, receipt, enactment and targeted behaviors in adherence studies.

Method: Five multi-disciplinary databases were searched to find reports of controlled trials testing pillboxes and medication adherence interventions in adults managing medications. Details of treatment fidelity: Design, Training, Delivery, Receipt, and Enactment were abstracted.

Discussion: A total of 38 articles reporting 40 studies were included. Treatment fidelity descriptions were often lacking, especially with regard to reporting receipt and enactment. This review demonstrates there are significant limitations in existing literature reporting on the use of pillboxes in medication adherence interventions.

Conclusions: These findings serve as a call to action to explicitly state pillbox intervention details. The lack of details provides challenges in translating which components of pillboxes work in influencing medication adherence behaviors and outcomes.

Key words: Medication adherence; treatment fidelity; Pillboxes; behavioral interventions

Review Chronic conditions affect 117 million adults across the United States (US) (Ward, Schiller, & Goodman, 2014), with the majority of these individuals taking at least one medication. Consistent medication adherence, defined as taking medication as prescribed, is a key treatment and important for managing disease progression (Jafar et al., 2003; Ruggenenti et al., 1998). Poor medication adherence can lead to disease progression, increased morbidity, and mortality. Between 20% and 50% of people are nonadherent to the prescribed medication regimen, that is, they do not have daily persistence in taking medications as prescribed, and this nonadherence may be responsible for up to 10% of all hospitalizations (Viswanathan et al., 2012). Good medication self-management includes knowing how to take medications as well as possessing the skills and demonstrating the behaviors to act on that knowledge (Bailey, Oramasionwu, & Wolf, 2013). Sustained medication adherence includes following prescribed medication regimens, adhering to dosing instructions, timely reporting of side effects, and developing habits to remember to take medications (Vrijens et al., 2012). Medication adherence thus requires remembering '*how'* to take medication (retrospective memory) and remembering '*when'* to take medications (prospective memory); both are components people may struggle with in managing medications.

Several systematic reviews have found evidence that pillboxes are effective interventions to support adherence to prescribed medication regimens (Boeni, Spinatsch, Suter, Hersberger, & Arnet, 2014; Conn et al., 2014; Zedler, Kakad, Colilla, Murrelle, & Shah, 2011). Pillboxes are containers that store scheduled doses of medications, and they are ubiquitous, sold nearly everywhere, and are inexpensive options to encourage medication-taking behaviors. They come in many different sizes,

shapes, and designs, ranging from simple single pillboxes used for one day to multiple boxes for multiple pills across multiple days.

Despite recognition that pillboxes may be effective in supporting medication adherence (Boeni et al., 2014; Conn et al., 2014), translating new knowledge from intervention studies into practice requires an understanding of salient intervention components. Such components consist of the “active ingredients” of the intervention designed to change behavior, that is, how the intervention was designed, delivered, and received and for whom it was successful. Intervention fidelity refers to methodological strategies that enhance confidence, reliability, and validity relative to intervention outcomes. Borrelli et al. (2005) outlined strategies to enhance intervention fidelity in behavioral interventions, specifically fidelity in the design, training, delivery, receipt, and enactment relative to these interventions. By understanding the targeted behaviors and behavioral change strategies linked with pillbox use, researchers and practitioners can increase their ability to judge the effectiveness of pillboxes and better integrate pillboxes into behavioral interventions.

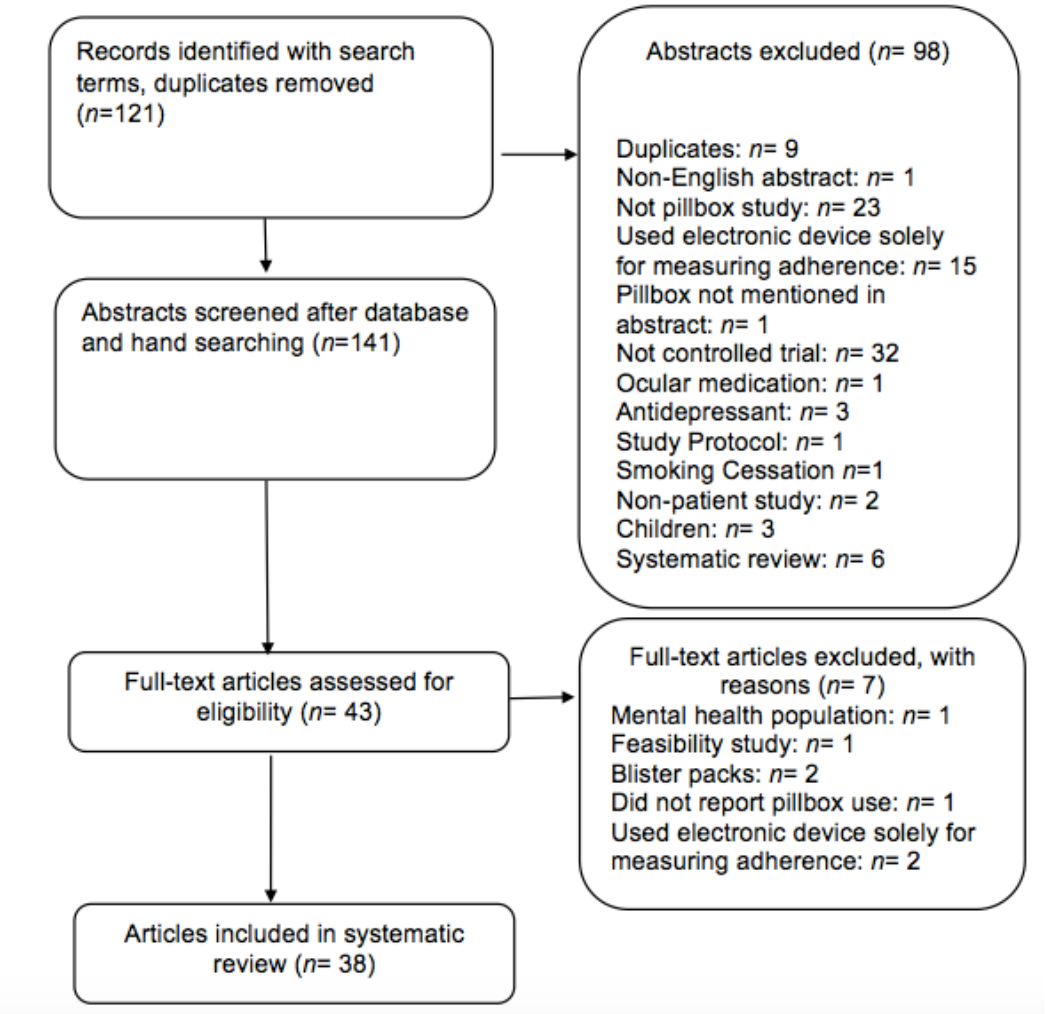
We undertook this review to understand the extent to which pillboxes have been integrated into intervention design, training of providers, delivery, receipt, and enactment and for which targeted behaviors pillboxes were used. The purpose of this review was to identify these intervention fidelity components in published primary intervention studies.

Methods

Search Strategies

We conducted a review with the assistance of an experienced reference librarian. Five multi-disciplinary databases (CINAHL, PubMed, Family & Society Studies Worldwide, PsycINFO, and SocINDEX) were searched to find literature related to medication adherence and the use of pillboxes. The final search terms used included all combinations of pill, prescription, medication, or drug AND box, container, case, organizer, or reminder, combined with the additional phrases, "medication compliance" or "medication adherence." Limits included scholarly, peer-reviewed journals, and journal articles. After removing non-English language abstracts, duplicate articles across databases, and non-academic periodicals, 141 results were returned from a combination of database searching and hand-searching references. See the flow diagram in Figure 1.

Figure 1. Study Flow Diagram



Inclusion Criteria

We included reports of controlled clinical intervention trials targeting increasing medication adherence in adults managing their own medications. We included both studies in which pillboxes were recommended or provided. Pillboxes were defined as containers with compartments designated for scheduled medications to be taken at a particular time or during a particular day.

Any studies conducted in patient populations in which medications could be deemed elective or temporary (e.g., smoking cessation, contraceptives, sexual dysfunction) were excluded. Studies focused on mental illness or psychiatric conditions

(e.g., major clinical depression, bipolar disorder) and populations with coexisting substance abuse were excluded from this review because of potential differences in factors influencing nonadherence such as the risk for substance abuse and beliefs about medications (Higashi et al., 2013; Jonsdottir et al., 2013). Trials using electronic adherence measuring devices (e.g., the Medication Event Monitoring System) were not included when the sole purpose of the device was for measurement rather than behavior change.

Data Coding and Quality Evaluation

Two independent reviewers selected articles for review. Once consensus was reached through discussion about which data to collect based on the study purpose and research questions, data were then extracted. Data included the author, publication year, study design, duration of the intervention and study follow-up, participant description (e.g., clinical conditions and number of medications), and whether the study was designed to treat and/or prevent nonadherence. A coding scheme was developed based on guidelines and best practices in intervention fidelity (Borrelli et al., 2005). Five categories of treatment fidelity have been identified to enhance the reliability and validity of findings from behavioral interventions (Borrelli et al., 2005): Design, Training, Delivery, Receipt, and Enactment. We define below each of these fidelity components in the context of pillbox components of interventions.

Design. Treatment design refers to the basic design of a trial as well as other components related to the content and dose of the intervention and control groups. For this review, important design components included descriptions about the treatment of the control and intervention groups and the components of the intervention. We

examined studies for inclusion criteria suggesting that patients were included in the study because of prior problems with nonadherence. These studies were classified as being “designed to treat nonadherence.” If studies were designed to promote adherence to medications and patients were not screened for previous history of nonadherence, they were classified as “designed to prevent nonadherence.” We extracted information to determine if the study was designed for all intervention group participants to receive the pillbox or if it was designed for all to receive a recommendation to use a pillbox. Studies in which pillboxes were recommended were included if criteria were established for when participants received a recommendation to use a pillbox. We specifically looked for explanations of when the pillbox was provided, under what circumstances pillboxes were recommended, and formal assessments developed based on these criteria. Treatment dose was evaluated based on number of contacts in which the pillbox was discussed, if applicable to the study design. Finally, we extracted whether interventionist qualifications were mentioned.

Training. Interventionist training and credentials were extracted when reported. This included assessing if or how reports described how providers were trained to deliver the pillbox component of the intervention, including training the interventionist on how to use the pillbox, when to use the pillbox, and when to recommend the pillbox. Descriptions were examined to determine if interventionist skill was measured following any training and if the interventionist was monitored across the duration of the study to maintain fidelity and consistency in intervention delivery.

Delivery. We looked for content indicating that a treatment manual or checklist was used in order to ensure the pillbox was delivered or recommended as intended.

We also examined whether the delivery of the pillbox intervention component mentioned how participants were taught how to use the pillbox.

Receipt. To determine treatment receipt, we extracted information suggesting that all participants who should have received a pillbox did receive the pillbox or, in the case of pillbox recommendations, that records were reported indicating how many people received a recommendation. We examined both descriptions and actual study findings reporting the number of participants receiving the pillbox or the recommendation. In addition to receiving the pillbox or a recommendation, we extracted whether study descriptions mentioned assessment of patients' skill acquisition specific to the pillbox. This included ensuring that the participant could use the pillbox as designed in the study.

Enactment. For pillbox enactment, we evaluated reports for descriptions of whether patients used the pillbox. If user feedback from participants was included, we noted this as well. Any descriptions that suggested the study assessed participants' use of the pillbox were reviewed. This included descriptions about the utility of, usability of, and/or satisfaction with the pillbox. We also looked at whether studies had assessed if participants actually used the pillbox, including reporting the number of participants who had used the pillbox and/or if a method was put in place to ensure the pillbox was used.

Results

A total of 38 articles reporting 40 studies met our inclusion criteria for this review. Study characteristics are described in Table 1.

Table 1: Study Characteristics

Author	Year	Country	Sample	Study Design	Intervention
Ascione	1984	USA	Cardiovascular/ Geriatrics (*N* = 158)	RCT	Multicomponent to improve attitudes, knowledge, & compliance behavior
Bosworth	2008	USA	Hypertension (*N* = 636)	RCT	Multicomponent tailored behavioral intervention
Burrelle	1987	USA	Hypertension (*N* = 16)	RCT	Multicomponent interdisciplinary compliance service
Calvert	2012	USA	CAD (*N* = 143)	RCT	Multicomponent patient-focused counseling intervention
Crome	1980	UK	Geriatrics Study 2: (*N*=14) Study 3: (*N*=26)	Study 2 - NRCT Study 3 - Cross-over RCT	Medication packaging intervention
Fairley	2003	Australia	HIV (*N* = 43)	RCT with "Stepped-Wedge" design*	Multicomponent adherence package
Farsaei	2011	Iran	Diabetes (*N* = 172)	RCT	Multicomponent educational intervention
Goldstein	2014	USA	Cardiovascular (HF) (*N* = 60)	2 x 2, open-label, RCT	Memory aid to improve medication adherence
Goujard	2003	France	HIV (*N* = 367)	RCT	Multicomponent educational intervention
Huang	2000	USA	TRACE: (*N* = 184) VITAL: (*N* = 297)	TRACE trial: Placebo-controlled, double-masked, 2x2	Multicomponent pill organizer & vitamin supplementation intervention

				factorial design VITAL trial: Placebo-controlled, double-masked pilot trial design	
Kalichman	2011	USA	HIV/AIDS (*N* = 40)	RCT	Behavioral self-management intervention
Kennedy	1990	USA	Elderly (*N* = 65)	RCT	Multicomponent self-care education intervention
Kripalani	2012	USA	Cardiac Diseases (*N* = 851)	RCT	Multicomponent pharmacist intervention for low literacy in cardiovascular disease
Laramee	2003	USA	CHF (*N*=287)	RCT	Multicomponent intervention with discharge planning, education, follow-up, and promotion of optimal medication management
Lee	1999	USA	Gastrointestinal Disorders (*N* = 125)	RCT	Multicomponent enhanced compliance program
Levensky	2006	USA	HIV (*N* = 54)	RCT	Multicomponent adherence counseling and education intervention
MacDonald	1997	UK	Chronic Disease (*N* = 165)	RCT	Multicomponent counseling interventions
Macintosh	2007	Canada	Cancer (*N* = 25)	Prospective, cross-over design	Medication packaging intervention
Maier	2006	Austria	Type 2 Diabetes (*N* = 2081)	RCT	Pocket-size tablet dispensing device intervention
McPherson-Baker	2000	USA	HIV (*N* = 42)	NRCT	Multicomponent behavioral intervention
Miaskowski	2004	USA	Cancer patients experiencing pain (*N* = 174)	RCT	Multicomponent PRO-SELF Pain Control Program

Moshkovska	2011	UK	Gastrointestinal Disease (*N* = 84)	RCT*	Multicomponent tailored patient preference intervention
Murray	1993	USA	Geriatrics (*N* = 31)	RCT	Medication packaging intervention
Nochowitz	2009	USA	Warfarin therapy (*N* = 13)	NRCT Prospective cohort study	Adherence aid intervention
Park	1992	USA	Chronic Disease (*N* = 61)	RCT	Cognitive support intervention
Peterson	1984	Australia	Epilepsy (N = 53)	RCT	Multicomponent compliance-improving strategies intervention
Porter	2014	USA	Hypertension (*N* = 60)	NRCT Prospective Pre/Post	Pill box clinic
Rehder	1980	USA	Hypertension (*N* = 100)	RCT	Multicomponent counseling & special prescription container interventions
Suárez-Varela	2009	Spain	Chronic Disease (*N* = 220)	RCT	Pillbox
Schmidt	2008	Germany	Heart Failure (*N* = 62)	NRCT Pre/Post	Tele-monitoring with electronic box
Suppapitiporn	2005	Thailand	Diabetes (*N* = 360)	RCT	Multicomponent drug counseling intervention
Sweeny	1989	UK	Chronic Disease (*N* = 103)	NRCT	Counseling intervention
Taylor	2003	USA	Chronic Disease (*N* = 69)	RCT	Multicomponent pharmaceutical care (educational) intervention
Traiger	1997	USA	Transplant (*N* = 41)	NRCT Pilot study	Multicomponent self-medication administration program
Tsuyuki	2004	Canada	Heart Failure (*N* = 276)	RCT	Multicomponent, multicenter disease management program
Wang	2010	China	HIV/AIDS (*N* = 116)	RCT	Multicomponent nurse-delivered home visits & phone call intervention
Winland-Brown	2000	USA	Chronic disease (*N* = 61)	RCT	Medication management approaches

Zillich	2005	USA	Uncontrolled BP (*N* = 125)	RCT	Multicomponent pharmacist - based home blood pressure monitoring program

Several different chronic conditions were studied including six conducted in HIV/AIDS, five in hypertension/uncontrolled blood pressure, two in gastrointestinal disorders, eight in cardiovascular-related conditions (coronary artery disease, cardiac disease, congestive heart failure, warfarin therapy), six in chronic conditions, three in diabetes, two in cancer, one each in transplant and epilepsy, two in vitamin supplementation, and four studies focused specifically on the older adult patient population. The subject sample sizes ranged from 13 to 2081 across studies. All, but one article, were written in English, and a trained medical interpreter provided translation service for the non-English article, which was written in Spanish. The five components of intervention fidelity assessed in this review are detailed in Table 2.

Table 2: Percentage of Articles (*N*=38) Reporting Use of Pillbox Intervention Fidelity Strategies

Treatment Fidelity Strategies	% (n) reporting*
Pillbox Intervention Design	
Designed to treat nonadherence	29% (11)
Designed for all intervention group participants to receive the pillbox	71% (24/34[a])
Criteria established for when to recommend a pillbox to participants	20% (2/10[b]); 5 NR
Provided pillbox description in studies that provided pillboxes (*n*=34)	55% (21);15 NR
Provided a pillbox to participants	89% (34); 1 NR
Interventionist qualifications	79% (30); 8 NR
Interventionist Training	
Interventionist training specific to the pillbox component (how to use, when to use, etc.),	5%(2); 35 NR;1 NA

Measured interventionist skill following training	6%(2); 34 NR; 2 NA
Mention of interventionist monitoring across study duration	7.9% (3); 35 NR
Delivery of Pillbox Intervention	
Included method to ensure the pillbox was delivered or recommended as intended (treatment manual, checklist)	7.9% (3); 35 NR
Mentioned participants were instructed/taught how to use the pillbox;	34% (19); 18 NR;1 NA
Receipt of Pillbox Intervention	
Reviewers had to assume the number of participants who received a pillbox based on study design	21% (8); 8 NR; 1 NA 55% (21)
Assessed patients' skill acquisition specific to the pillbox	21% (8); 29 NR; 1 NA;
Enactment of Pillbox	
Assessed utility, usability, and/or satisfaction	32% (12); 26 NR
Reported number who used pillbox/method to ensure pillbox was used;	16% (6)

Note: NR - Not reported; NA - Not applicable based on study design;
[a]in studies that provided pillboxes
[b]in studies that recommended pillboxes

Intervention Design. Pillbox interventions were largely designed to prevent nonadherence. Eleven studies (Burrelle, 1986; Fairley et al., 2003; Kalichman et al., 2011; Laramee, Levinsky, Sargent, Ross, & Callas, 2003; Levensky, 2006; McPherson-Baker et al., 2000; Morales, 2009; Nochowitz, Shapiro, Nutescu, & Cavallari, 2009; Schmidt, Sheikzadeh, Beil, Patten, & Stettin, 2008; Taylor, Byrd, & Krueger, 2003; Winland-Brown & Valiante, 2000) were designed to treat nonadherence and used nonadherence as screening or inclusion criteria for participation in the study. Self-report was most often used to measure nonadherence. The 4-item Morisky Medication Adherence Scale (MMAS-4) questionnaire was used in two studies (Burrelle, 1986; Fairley et al., 2003), and one study used a version of the MMAS(Morales, 2009) whereas two studies assessed self-report of missed doses over the preceding month

(Fairley et al., 2003; Kalichman et al., 2011). Laramee et al.(2003) included both those at risk for nonadherence and those with a past history of such, although how this assessment was made was not explained. McPherson-Baker et al. and Taylor et al. used medication-refill patterns as indicators of nonadherence. Two studies used the medical record to screen for a documented history of nonadherence(Taylor et al., 2003; Winland-Brown & Valiante, 2000). Winland-Brown et al. and McPherson-Baker et al. included hospitalization that could be related to medication mismanagement as an indicator of nonadherence.

Thirty-four studies provided pillboxes to participants (Ascione & Shimp, 1984; Burrelle, 1986; Calvert et al., 2012; Crome, Akehurst, & Keet, 1980; Fairley et al., 2003; Farsaei, Sabzghabaee, Zargarzadeh, & Amini, 2011; Goldstein et al., 2014; Goujard et al., 2003; Huang, Maguire, Miller, & Appel, 2000; Kennedy, 1990; Kripalani et al., 2012; Laramee et al., 2003; Lee et al., 1999; Macdonald, MacDonald, & Phoenix, 1977; Macintosh, Pond, Pond, Leung, & Siu, 2007; Maier, Mustapic, Schuster, Luger, & Eher, 2006; McPherson-Baker et al., 2000; Morales, 2009; Moshkovska et al., 2011; Murray, Birt, Manatunga, & Darnell, 1993; Nochowitz et al., 2009; Park, Morrell, Frieske, & Kincaid, 1992; Peterson, McLean, & Millingen, 1984; Porter, Taylor, Yabut, & Al-Achi, 2014; Rehder, McCoy, Blackwell, Whitehead, & Robinson, 1980; Schmidt et al., 2008; Suppapitiporn, Chindavijak, & Onsanit, 2005; Sweeney, Dixon, & Sutcliffe, 1989; Traiger & Bui, 1997; Tsuyuki et al., 2004; Wang et al., 2010; Winland-Brown & Valiante, 2000). Crome et al.(1980) and Huang et al.(2000) each reported on two pillbox studies), and five studies recommended pillboxes (Bosworth et al., 2008; Kalichman et al., 2011; Levensky, 2006; Taylor et al., 2003; Zillich, Sutherland, Kumbera, & Carter, 2005).

Kalichman et al.(2011) recommended a pillbox when participants found it difficult to manage medications or if they kept pillboxes in multiple places, whereas Bosworth et al.(2008) recommended a pillbox when participants reported difficulty remembering to take medications. Sweeny et al.(1989) provided a pillbox to participants if the pharmacist believed the participant could benefit from it, but no criteria about how this judgment was made were reported. One article did not include details about whether the pillbox was provided or recommended as part of the study (Miaskowski et al., 2004). Of those studies in which a pillbox was provided, four(Macintosh et al., 2007; Murray et al., 1993; Rehder et al., 1980; Winland-Brown & Valiante, 2000) prefilled the pillboxes with the participants' medications and 11 required participants to fill their own pillboxes (Ascione & Shimp, 1984; Burrelle, 1986; Huang et al., 2000; Laramee et al., 2003; Lee et al., 1999; Maier et al., 2006; McPherson-Baker et al., 2000; Park et al., 1992; Porter et al., 2014; Traiger & Bui, 1997; Wang et al., 2010). Nochowitz et al. (2009) filled pillboxes for participants if they brought their medications to the study appointment; otherwise, participants were required to fill their own. Of the 34 studies that provided pillboxes, 29 studies were designed for intervention group participants to automatically receive the pillbox as part of the intervention; these were reported in 27 articles (Ascione & Shimp, 1984; Burrelle, 1986; Calvert et al., 2012; Crome et al., 1980; Farsaei et al., 2011; Goldstein et al., 2014; Goujard et al., 2003; Huang et al., 2000; Kripalani et al., 2012; Lee et al., 1999; Macdonald et al., 1977; Macintosh et al., 2007; Maier et al., 2006; McPherson-Baker et al., 2000; Morales, 2009; Murray et al., 1993; Nochowitz et al., 2009; Park et al., 1992; Peterson et al., 1984; Porter et al., 2014; Rehder et al., 1980; Schmidt et al., 2008; Suppapitiporn et al., 2005; Traiger & Bui,

1997; Tsuyuki et al., 2004; Wang et al., 2010; Winland-Brown & Valiante, 2000). In the other five studies, participants may have received a recommendation for or offered the use of a pillbox, and if they accepted the offer, they were then provided with a specific pillbox to use (Fairley et al., 2003; Kennedy, 1990; Laramee et al., 2003; Moshkovska et al., 2011; Sweeney et al., 1989).

Eight of the above studies used either a subgroup that was provided with a pillbox as part of the intervention or had an additional treatment arm as part of the study (Ascione & Shimp, 1984; Goldstein et al., 2014; Macdonald et al., 1977; Murray et al., 1993; Park et al., 1992; Rehder et al., 1980; Suppapitiporn et al., 2005; Winland-Brown & Valiante, 2000). Most studies (*n* = 31) included a usual care control group as part of the study design. In two studies included in this review there were reports of potential contamination, with 19 people in one study from the control group attending the intervention education sessions where pillboxes were distributed (Goujard et al., 2003), and in another study, 39% (*n*=7) of the attention control group reported using pillboxes (Kalichman et al., 2011). Fairley et al.(2003) reported that 42% (18/43) of study participants reported already using pillboxes at enrollment. Other studies in this review did not report if they evaluated whether the control group participants used pillboxes. With regard to treatment dose, there were some reports of at least one contact session that specifically covered pillbox use (Farsaei et al., 2011; Goujard et al., 2003; Lee et al., 1999; Miaskowski et al., 2004; Park et al., 1992; Porter et al., 2014; Rehder et al., 1980; Wang et al., 2010).

Interventionist Qualifications and Training. Of those studies reporting the qualifications of the interventionist, most used exclusively nurses (Bosworth et al., 2008;

Crome et al., 1980; Fairley et al., 2003; Kennedy, 1990; Laramee et al., 2003; Miaskowski et al., 2004; Morales, 2009; Traiger & Bui, 1997; Wang et al., 2010) (*n* = 9) or exclusively pharmacists(Ascione & Shimp, 1984; Calvert et al., 2012; Farsaei et al., 2011; Kripalani et al., 2012; Lee et al., 1999; Macdonald et al., 1977; McPherson-Baker et al., 2000; Murray et al., 1993; Porter et al., 2014; Rehder et al., 1980; Suppapitiporn et al., 2005; Sweeney et al., 1989; Taylor et al., 2003; Tsuyuki et al., 2004; Zillich et al., 2005) (*n* = 15), and the remaining few (*n* = 6) used a variety of and/or different combinations of personnel (e.g., nurses, social workers, nutritionists, physicians) (Burrelle, 1986; Goujard et al., 2003; Kalichman et al., 2011; Levensky, 2006; Moshkovska et al., 2011; Schmidt et al., 2008). Nochowicz (2009) did not specifically report interventionist qualifications, but the intervention was carried out in a pharmacist-run clinic and all investigators were pharmacists. Only two articles reported whether these interveners underwent training in delivering the intervention specific to the pillbox component (Bosworth et al., 2008; Traiger & Bui, 1997).

Delivery of the Intervention. Ten articles reported that some type of content about using the pillbox was included in the intervention, although this content varied widely (Kalichman et al., 2011; Lee et al., 1999; Morales, 2009; Nochowitz et al., 2009; Park et al., 1992; Peterson et al., 1984; Porter et al., 2014; Rehder et al., 1980; Schmidt et al., 2008; Taylor et al., 2003). For example, Kalichman et al.(2011) used pillboxes along with self-regulation counseling in which pillboxes were discussed with participants to support medication management skills such as planning and organizing of medications in routines, but no specific details were provided. Lee et al.(1999) used a pharmacist to teach participants to fill a pocket-sized pillbox, but no details were provided. Porter et al.

(2014) also used a pharmacist, and when patients and caregivers did not fill the pillbox correctly the pharmacist then read the labels on the bottles while observing and, if necessary, correcting the participants filling the pillboxes. Two studies mentioned that participants were taught how to use the pillbox, including how to fill the box (Park et al., 1992; Porter et al., 2014). One study used a home nurse to assist with the pillbox filling if the patient was not capable of it (Sweeney et al., 1989). Schmidt et al. (2008) used a pillbox with tele-monitoring capabilities and an alarm; the instructions on how to use the pillbox were related to how to silence the alarm by opening the box and how to ensure the data were electronically recorded. On the other hand, Maier and colleagues (2006) reported they purposely did not include content about how to use the pillbox.

Receipt of the Intervention. It was difficult to extract the number of people receiving the intervention. Eight articles specifically mentioned the number of participants receiving the pillbox; however, most of the receipt classification was assumed based on study design (Fairley et al., 2003; Kalichman et al., 2011; Levensky, 2006; Macdonald et al., 1977; Maier et al., 2006; Moshkovska et al., 2011; Nochowitz et al., 2009; Park et al., 1992). As an example, in Levensky and colleagues' study (2006), 50% of intervention participants (*n* = 12) were given a recommendation to use pillboxes, and this recommendation was made at three time points consistent with the study design. However, it is unclear if these were the same 12 people or a combination of different people in the intervention group. There was also variation in the reporting of assessment of patient skill in using the pillbox. For example, Crome et al. (1980) reported the time it took for patients to acquire skill, whereas Sweeney et al. (1989)

mentioned patients' expression of concern about filling pillboxes. Two studies permitted participants to self-select pillbox use (Fairley et al., 2003; Moshkovska et al., 2011).

Enactment of the Intervention. Very few studies evaluated if participants actually used the pillbox. In particular, only six articles specifically reported enactment or used a design that required the pillbox to be used because of the nature of the intervention (Burrelle, 1986; Crome et al., 1980; Goldstein et al., 2014; Levensky, 2006; Macdonald et al., 1977; Macintosh et al., 2007). Levensky (2006), Burelle et al.(1986) and MacIntosh et al. (2007) counted the number of pills remaining in the pillbox to evaluate medication adherence and therefore it is assumed the pillbox was used. Nochowitz et al. (2009) also performed a pill count when participants brought their pillboxes to the clinic, but not all participants brought their pillboxes to the clinics and therefore it is unclear how many participants used the pillbox. Crome et al.(1980) used a specific pillbox (Dosette) and participants had to use the box appropriately in order to progress in the study; these participant numbers were provided by the authors. Goldstein et al. (2014) utilized an electronic sensing pillbox that recorded opening and closing of the device and therefore was able to demonstrate use. MacDonald reported pillbox use and specifically that 40% (*n*=6) of users had stopped using the pillbox over the 12 weeks of the intervention.

Approximately one third of the studies assessed patients' experiences in using the pillbox. Pillbox use was mentioned as being helpful in some studies and in others use dwindled over time. For example, Levensky et al.(2006) reported pillbox receipt and use for three time points and whether the pillbox recommendations were fully or partially implemented. At the first time point, 100% of participants who had been given

recommendations for pillboxes reported they fully used them, but this number declined over the 6-week time period and had further declined by the last study time point at 20 months out, with approximately half fully implementing the intervention and half partially implementing the pillbox intervention. In one study,(Lee et al., 1999), that included a multicomponent intervention consisting of pharmacist-delivered education, a calendar, and pillbox, participants found the pillbox component to be the most helpful.

Discussion

The present review sought to describe the extent to which intervention fidelity components have been integrated into interventions using pillboxes. Of the 40 studies reported in the 38 articles included in our review, there were varying degrees of detail reported about pillbox intervention fidelity. These differences in key intervention details make it difficult to know if and when pillboxes are an effective component of medication adherence-related interventions, limit replication of studies, and limit translation of study findings into practice.

Intervention fidelity is critical to interpreting studying findings with confidence and translating these into practice. There was significant disparity and heterogeneity found in intervention descriptions with respect to intervention fidelity. This leads to challenges in synthesizing study findings in any meaningful way for translation into practice. For example, less than 20% of the articles reported a method to ensure that participants actually used the pillbox component of the intervention. Therefore, it is difficult to determine whether the pillbox played an integral role in influencing medication adherence behaviors and outcomes. Moreover, few of the articles reported the number of participants who received a pillbox and how many were still using the pillbox at the

end of the study. We suggest that reporting the numbers of participants receiving treatment and enacting treatment is as important as reporting attrition or performing an intention-to-treat analysis. Without reporting receipt and enactment numbers, conclusions about the effectiveness of using pillboxes are limited.

In articles that described the pillbox as part of the intervention, we assumed that all participants did in fact receive the pillbox, which may not be a valid assumption. Although this might be inferred from the number of people in the intervention group, it also relies on the study being designed to ensure that the study protocol was in fact carried out the way it was planned, and these details were often lacking. Therefore, it cannot be readily assumed that those who should have received the pillbox did so, especially given the lack of outcome measures that accounted for the sample size receiving the pillbox. This highlights the need for authors to more clearly articulate intervention fidelity components so that conclusions can be based on actual findings and not assumptions.

Articles included in our review specifically identified use of compartmentalized containers or identified the brand name of the pillbox, which allowed us to confirm the study met inclusion criteria. However, this relied on authors including these details in their publication, details critical to advancing the science. Based on our inclusion criteria, articles needed to report use of a multi-compartment storage container or provide enough details to confirm this requirement (brand name, picture, etc.) and blister or foil packaging were not included. Articles included in our review may differ from articles included in past reviews (Conn et al., 2014) based on our inclusion criteria. One important factor that may explain this difference is that the researchers in these

other articles contacted authors to gain details on studies when specific details were not included, and we did not use this approach as our focus was on the extent to which these descriptions were reported in the literature. We only focused our review on descriptions reported in the literature because these descriptions contain details that affect both interpretation of study findings and translation of the intervention into practice (Bellg et al., 2004; Borrelli, 2011).

Differences in how pillboxes were used to support medication taking were noted across studies. First, some interventions were designed to treat nonadherence whereas some were designed to prevent nonadherence. This difference in study design may be important in deciding which patient populations may most benefit from use of pillboxes or pillboxes may be effective for everyone, but that is unclear given the lack of detail related to treatment fidelity. Second, no article reported if participants' past use of pillboxes was assessed. The literature suggests that as many as 50-77%[47,48] of people report using pillboxes on their own. In light of these statistics, one potential limitation of using usual care group comparisons is that many of those in the usual care groups are likely to be using pillboxes on their own, therefore, highlighting the need to assess for current pillbox use in comparison groups.

It is unclear how the pillbox was used as a strategy to support medication management and adherence. Approximately half of the articles in our review stated that pillboxes were used as memory aids. For example, Park et al.(Park et al., 1992) found that in the older adult population errors of omission were frequent, but use of a pillbox and reminder calendar may help reduce cognitive effort and support prospective memory,[37] that is, remembering when to take medication. However, it is unclear which

design features of a pillbox actually support prospective memory. For example, an alarm or placement in sight of a pillbox might cue a person to take the medication, whereas an empty pillbox container might cue a person that the medication has been taken (retrospective memory). These memory-related components that support medication taking operate in different ways, that is, the active ingredients of changing behaviors rely upon different understandings of the specific behaviors that require changing in order to achieve medication adherence. Participants reported that pillboxes were helpful; however, the salient features of the pillboxes and the actual medication-taking behaviors that were supported by the use of a pillbox are unknown.

Limitations

The findings of this review should be interpreted in light of some limitations. Some of these studies were published prior to systematic guidelines for reporting randomized clinical trials such as the CONSORT guidelines(Begg et al., 1996) and the publication about components of treatment fidelity.(Borrelli et al., 2005) For this reason, these details may have been lacking in some articles. We also marked treatment fidelity characteristics as “not reported” in many cases rather than contacting the study investigators to obtain these details. In order to facilitate scientific advancement and prevent readers from making assumptions, we believe it is imperative for authors to publish details about their interventions such as the specific targeted behaviors that pillboxes serve to mediate and the intervention fidelity components. We cannot rely on systematic review investigators to track down and report these details.

Implications for Research

Future research should seek to identify the behaviors that are supported by use of pillboxes, which pillbox design features support those behaviors, and which patient attributes might best be suited to specific behavior change techniques using a pillbox. This information would be helpful to establish clear indications for when a pillbox may be effective and for whom. In order to conduct this research, medication adherence researchers will need valid and reliable measures of medication adherence applicable to those who use pillboxes. We propose that pillbox intervention fidelity components be incorporated into well-designed trials and that fidelity components be reported in future publications to facilitate translation into practice.

Conclusions

This review demonstrates there are significant limitations in the existing literature reporting on the use of pillboxes in medication adherence interventions. The effectiveness of pillboxes cannot be fully determined if intervention components such as intervention fidelity are not clearly described within studies. Failure of authors to do this limits the advancement of science. Based on the studies reviewed herein, there is little evidence about the effectiveness of pillboxes as an intervention to support medication management and medication adherence. In order to determine the effects of a treatment on an outcome, methodological strengths including treatment fidelity must be considered. Based on the current evidence, few studies have been of high enough quality to warrant drawing conclusions about the effectiveness of pillboxes in supporting specific medication management and adherence behaviors. Furthermore, there is limited reporting in the literature of the five components of intervention fidelity with pillboxes, thus limiting generalizability of the study findings. Despite some articles

reporting that patients found the pillboxes to be useful in supporting medication taking, the way in which the pillbox helped to support medication-taking behaviors remains unknown. For example, if the pillbox helped participants to remember to take medications, which pillbox design features, if any, contributed to remembering, how did the participants use the design features to support medication-taking behaviors, and did the design features vary between pillboxes such that some pillboxes might be more effective than others? Before moving to intervention research, it is imperative to establish which medication-taking behaviors are supported by use of a pillbox. This requires understanding how people interact with their pillboxes and then developing theory-based interventions. These findings serve as a call to action for researchers to explicitly state pillbox intervention details. The lack of details provides challenges for clinicians, care providers and researchers to determine how pillboxes work in influencing medication adherence behaviors and outcomes. More high quality, well powered, and theory-based studies paying attention to intervention fidelity are needed in order to determine the effectiveness of pillboxes in supporting medication adherence.

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